Supplementary material

Section S1 Inclusion and exclusion criteria

Section S2 Trial oversight

Section S3 Sites

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Section S5 Health-related Quality of Life

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Section S7 Protocols and statistical analysis plans:

Original protocol (version 2.0, approved before the first site opened)

Final protocol (version 9.0)

Version control document (summary of changes)

Original statistical analysis plan (version 1.0)

Second and final statistical analysis plan (version 2.0, changes listed in section 1.6)

S1 Inclusion and exclusion criteria

Protocol version 2 (approved 18.8.15, before recruitment started)

Inclusion criteria

1. Patients (18 years or over) who have a native AVF in the arm that has been used for haemodialysis for at least 12 dialysis sessions
2. An indication for a fistuloplasty as determined by the local clinical team
3. The access circuit is free of synthetic graft material or stents
4. A reduction of vessel diameter of ≥ 50% measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon
5. A residual stenosis ≤ 30% after plain balloon fistuloplasty

Exclusion criteria

1. Patient unable to give informed consent
2. Patient unwilling or unable to comply with all study-related procedures
3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure
4. Synchronous venous lesion, with a reduction of vessel diameter of ≥ 50% measured angiographically, in the same access circuit
5. Location of stenosis beyond the thoracic inlet
6. Thrombosed (failed) dialysis circuit at time of treatment
7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children, within two years of study treatment
8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated
9. Known hypersensitivity or contraindication to paclitaxel

Protocol version 5 (approved 8.4.16)

Inclusion criteria 1 amended:

1. Patients (18 years or over) who have a native AVF in the arm

Protocol version 6 (approved 31.8.16)

Inclusion criteria 6 added:

6. A treatment segment, containing one or more lesions, which can be treated with ≤120 mm of a single drug-coated balloon.

Exclusion criteria 4 amended:

4. One or more lesions outside the treatment segment, with a reduction of vessel diameter of ≥ 50% measured angiographically, in the same access circuit.

Protocol version 7 (approved 21.3.17)

Exclusion criteria 4 amended again:

4. One or more lesions outside the treatment segment, with a reduction of vessel diameter of ≥ 50% measured angiographically, in the same access circuit. The patient will also be excluded if any lesions outside the treatment segment are treated even if these are <50%

S2 Trial Oversight

Data Monitoring Committee

Chair	Watson, Christopher[1]	University of Cambridge	25/04/2017 - current
Member	Hiemstra[2] Thomas	University of Cambridge	Added 11/08/2018 - current
Member	Reading, Isabel[3]	University of Southampton	Original Member
Resigned Chair	Oliviera, David[2]	St George's University of London	Original - 25/04/2017
Resigned Member	Ettles, Duncan[4]	Hull and East Yorkshire Hospitals NHS Trust	Original - 25/04/2017
Resigned Member	Wigham[4], Andrew	John Radcliffe Hospital NHS Trust	25/04/2017 - 11/08/2018

Trial steering committee

Chair	Haynes, Richard[2]	University of Oxford	Original Member
Member	McGrath, Andrew[4]	Beaumont Hospital, Dublin, Ireland	Added 25/04/2017 - current
Member	Troxler, Max[1]	Leeds Teaching Hospital NHS Trust	Original Member
Public Member	Palmer, Nick[5]	National Kidney Federation	Original Member
Member	Mitra, Sandip[2]	Manchester University NHS Foundation Trust	Original Member
Resigned Member	Patel, Uday[4]	St George's Healthcare NHS Trust	22/07/2016 - 25/04/2017
Resigned Member	Littler, Peter[4]	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	Original Member - 22/07/2016

1 Transplant and vascular access surgeon
2 Nephrologist
3 Statistician
4 Interventional radiologist
5 Patient representative

S3 Sites

Table: Hospital sites (radiologists per site)

Radiologist performing the treatment was a minimisation factor.

	Paclitaxel-coated balloon (n=106)	Standard balloon (n=106)
1. Bradford (1)	2	2
2. Cardiff (2)	5	3
3. Canterbury (2)	14	16
4. Edinburgh (2)	3	-
5. Gloucester (2)	8	8
6. Guy's (9)	21	16
7. Hull (3)	4	5
8. King's (4)	4	8
9. Leicester (1)	2	2
10. Lister (2)	11	10
11. Portsmouth (2)	5	2
12. Devon (2)	4	3
13. Royal London (1)	1	3
14. Reading (2)	5	4
15. Royal Free (3)	3	5
16. Preston (2)	2	3
17. Brighton (1)	1	1
18. Sheffield (2)	1	1
19. St George's (1)	1	2
20. St Helier (1)	9	12

S4 Baseline smoking and renal replacement therapy history of the intention-to-treat population

		Paclitaxel-coated balloon (n=106)	Standard balloon (n=106)
		n (%) unless stated	
Patient smoking history (n=211)	Current	12 (11.4)	16 (15.1)
	Former	37 (35.2)	33 (31.1)
	Never	56 (53.3)	57 (53.8)
Total accumulated time patient has spent on haemodialysis (months; quartiles) (n=211)	0-6 months	29 (27.4)	26 (24.8)
	7-17 months	20 (18.9)	31 (29.5)
	18-39 months	31 (29.2)	23 (21.9)
	40-198 months	26 (24.5)	25 (23.8)
Previous renal transplant(s)	Yes	9 (8.5)	15 (14.2)
Total accumulated time with a functional renal transplant (months) (n=22)	median (IQR)	77 (25-174)	73.5 (4-204)
Spent time on peritoneal dialysis	Yes	13 (12.3)	19 (17.9)
Total accumulated time patient has spent on peritoneal dialysis (months) (n=32)	median (IQR)	11 (4-24)	31 (12-67)

S5 Health-related Quality of Life (HRQoL)

		Paclitaxel-coated balloon (n=106)	Standard balloon (n=106)
Baseline (n=196)			
EQ-5D-5L [Description of health today]			
Mobility	No problems	29 (28.7)	27 (28.4)
	Slight problems	23 (22.8)	27 (28.4)
	Moderate problems	29 (28.7)	20 (21.1)
	Severe problems	13 (12.9)	18 (18.9)
	Unable to walk about	7 (6.9)	3 (3.2)
Self-Care	No problems	68 (67.3)	60 (63.2)
	Slight problems	17 (16.8)	18 (18.9)
	Moderate problems	7 (6.9)	10 (10.5)
	Severe problems	5 (5.0)	5 (5.3)
	Unable to wash/dress myself	4 (4.0)	2 (2.1)
Usual Activities	No problems	28 (27.7)	32 (33.7)
	Slight problems	32 (31.7)	26 (27.4)
	Moderate problems	22 (21.7)	22 (23.2)
	Severe problems	10 (9.9)	10 (10.5)
	Unable to do usual activities	9 (8.9)	5 (5.3)
Pain/Discomfort	None	44 (43.6)	27 (28.4)
	Slight	28 (27.7)	31 (32.6)
	Moderate	18 (17.8)	29 (30.5)
	Severe	7 (6.9)	7 (7.4)
	Extreme	4 (4.0)	1 (1.1)
Anxiety/Depression	None	66 (65.3)	47 (49.5)
	Slight	20 (19.8)	29 (30.5)
	Moderate	12 (11.9)	17 (17.9)
	Severe	1 (1.0)	2 (2.1)
	Extreme	2 (2.0)	-
Health today (VAS) (0=worst imaginable; 100=best imaginable)	mean (SD)	66.3 (19.4) n=99	63.6 (22.3) n=95
POS-S Renal [How have each of the 17 symptoms affected them and how they have felt over past week] (n=191)			
Total score (0=not at all; 4=overwhelmingly) Min=0 Max=68	mean (SD)	12.9 (9.3) n=97	13.7 (9.4) n=94

EQ-5D-5L post randomisation			
6-months (n=145)			
Mobility	No problems	17 (24.3)	19 (25.3)
	Slight problems	21 (30.0)	19 (25.3)
	Moderate problems	11 (15.7)	19 (25.3)
	Severe problems	14 (20.0)	12 (16.0)
	Unable to walk about	7 (10.0)	6 (8.0)
Self-Care	No problems	44 (62.9)	42 (56.0)
	Slight problems	10 (14.3)	13 (17.3)
	Moderate problems	5 (7.1)	11 (14.7)
	Severe problems	8 (11.4)	7 (9.3)
	Unable to wash/dress myself	3 (4.3)	2 (2.7)
Usual Activities	No problems	26 (37.1)	24 (32.0)
	Slight problems	15 (21.4)	24 (32.0)
	Moderate problems	11 (15.7)	12 (16.0)
	Severe problems	11 (15.7)	11 (14.7)
	Unable to do usual activities	7 (10.0)	4 (5.3)
Pain/Discomfort	None	28 (40.0)	15 (20.3)
	Slight	18 (25.7)	25 (33.8)
	Moderate	14 (20.0)	22 (29.7)
	Severe	8 (11.4)	10 (13.5)
	Extreme	2 (2.9)	2 (2.7)
Anxiety/Depression	None	40 (57.1)	36 (48.0)
	Slight	16 (22.9)	31 (41.3)
	Moderate	10 (14.3)	6 (8.0)
	Severe	3 (4.3)	2 (2.7)
	Extreme	1 (1.4)	-
12-months (n=95)			
Mobility	No problems	17 (35.4)	9 (19.1)
	Slight problems	10 (20.8)	16 (34.0)
	Moderate problems	9 (18.8)	13 (27.7)
	Severe problems	7 (14.6)	8 (17.0)
	Unable to walk about	5 (10.4)	1 (2.1)
Self-Care	No problems	31 (64.6)	28 (59.6)
	Slight problems	10 (20.8)	12 (25.5)
	Moderate problems	2 (4.2)	6 (12.8)
	Severe problems	3 (6.3)	1 (2.1)
	Unable to wash/dress myself	2 (4.2)	-
Usual Activities	No problems	17 (35.4)	13 (27.7)
	Slight problems	15 (31.3)	13 (27.7)

	Moderate problems	5 (10.4)	14 (29.8)
	Severe problems	4 (8.3)	6 (12.8)
	Unable to do usual activities	7 (14.6)	1 (2.1)
Pain/Discomfort	None	20 (41.7)	15 (31.9)
	Slight	12 (25.0)	15 (31.9)
	Moderate	10 (20.8)	11 (23.4)
	Severe	3 (6.3)	5 (10.6)
	Extreme	3 (6.3)	1 (2.1)
Anxiety/Depression	None	28 (58.3)	24 (51.1)
	Slight	12 (25.0)	19 (40.4)
	Moderate	6 (12.5)	4 (8.5)
	Severe	-	-
	Extreme	2 (4.2)	-

Data are presented as *n (%)* unless otherwise specified; VAS: visual analogue scale

S6 List of adverse events

Treatment group	Adverse event category	Serious Adverse Event	Intensity
Paclitaxel-coated balloon	Insertion of CVC	0. No	1. Mild
Paclitaxel-coated balloon	Insertion of CVC	0. No	1. Mild
Paclitaxel-coated balloon	Insertion of CVC	0. No	1. Mild
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	1. Yes	2. Moderate
Paclitaxel-coated balloon	Thrombosed access	0. No	1. Mild
Paclitaxel-coated balloon	Thrombosed access	1. Yes	1. Mild
Paclitaxel-coated balloon	Thrombosed access	1. Yes	1. Mild
Paclitaxel-coated balloon	Thrombosed access	1. Yes	2. Moderate
Paclitaxel-coated balloon	Thrombosed access	1. Yes	2. Moderate
Paclitaxel-coated balloon	Thrombosed access	1. Yes	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	0. No	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	0. No	3. Severe
Paclitaxel-coated balloon	Access-related (other)	0. No	3. Severe
Paclitaxel-coated balloon	Access-related (other)	1. Yes	1. Mild
Paclitaxel-coated balloon	Access-related (other)	1. Yes	1. Mild
Paclitaxel-coated balloon	Access-related (other)	1. Yes	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	1. Yes	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	1. Yes	3. Severe
Paclitaxel-coated balloon	Access-related (other)	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	0. No	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	0. No	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild

Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Gastrointestinal	1. Yes	3. Severe
Paclitaxel-coated balloon	Foot disease	1. Yes	2. Moderate
Paclitaxel-coated balloon	Foot disease	1. Yes	3. Severe
Paclitaxel-coated balloon	Foot disease	1. Yes	3. Severe
Paclitaxel-coated balloon	Fall/syncope	1. Yes	1. Mild
Paclitaxel-coated balloon	Fall/syncope	1. Yes	2. Moderate
Paclitaxel-coated balloon	Fall/syncope	1. Yes	2. Moderate
Paclitaxel-coated balloon	Fall/syncope	1. Yes	2. Moderate
Paclitaxel-coated balloon	Musculoskeletal	1. Yes	2. Moderate
Paclitaxel-coated balloon	Musculoskeletal	1. Yes	2. Moderate
Paclitaxel-coated balloon	Musculoskeletal	1. Yes	3. Severe
Paclitaxel-coated balloon	Hypertension	1. Yes	3. Severe
Paclitaxel-coated balloon	Bacteraemia	1. Yes	2. Moderate
Paclitaxel-coated balloon	Bacteraemia	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cutaneous	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	0. No	1. Mild
Paclitaxel-coated balloon	Other	0. No	1. Mild
Paclitaxel-coated balloon	Other	0. No	1. Mild
Paclitaxel-coated balloon	Other	0. No	1. Mild
Paclitaxel-coated balloon	Other	0. No	3. Severe
Paclitaxel-coated balloon	Other	1. Yes	1. Mild
Paclitaxel-coated balloon	Other	1. Yes	1. Mild
Paclitaxel-coated balloon	Other	1. Yes	1. Mild

Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	2. Moderate
Standard balloon	Insertion of CVC	0. No	2. Moderate
Standard balloon	Insertion of CVC	0. No	2. Moderate
Standard balloon	Insertion of CVC	1. Yes	1. Mild
Standard balloon	Thrombosed access	0. No	2. Moderate
Standard balloon	Thrombosed access	1. Yes	1. Mild
Standard balloon	Thrombosed access	1. Yes	2. Moderate
Standard balloon	Thrombosed access	1. Yes	2. Moderate
Standard balloon	Thrombosed access	1. Yes	3. Severe
Standard balloon	Access-related (other)	0. No	1. Mild
Standard balloon	Access-related (other)	0. No	1. Mild
Standard balloon	Access-related (other)	0. No	1. Mild

Standard balloon	Access-related (other)	0. No	2. Moderate
Standard balloon	Access-related (other)	0. No	2. Moderate
Standard balloon	Access-related (other)	1. Yes	2. Moderate
Standard balloon	Access-related (other)	1. Yes	2. Moderate
Standard balloon	Access-related (other)	1. Yes	2. Moderate
Standard balloon	Access-related (other)	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	0. No	1. Mild
Standard balloon	Cardiovascular/respiratory	0. No	1. Mild
Standard balloon	Cardiovascular/respiratory	1. Yes	1. Mild
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Standard balloon	Gastrointestinal	0. No	1. Mild
Standard balloon	Gastrointestinal	0. No	1. Mild
Standard balloon	Gastrointestinal	1. Yes	1. Mild
Standard balloon	Gastrointestinal	1. Yes	2. Moderate
Standard balloon	Gastrointestinal	1. Yes	2. Moderate
Standard balloon	Gastrointestinal	1. Yes	2. Moderate
Standard balloon	Gastrointestinal	1. Yes	2. Moderate
Standard balloon	Gastrointestinal	1. Yes	2. Moderate
Standard balloon	Gastrointestinal	1. Yes	2. Moderate
Standard balloon	Gastrointestinal	1. Yes	2. Moderate
Standard balloon	Foot disease	0. No	2. Moderate
Standard balloon	Foot disease	0. No	2. Moderate
Standard balloon	Foot disease	1. Yes	2. Moderate

Standard balloon	Foot disease	1. Yes	2. Moderate
Standard balloon	Foot disease	1. Yes	3. Severe
Standard balloon	Fall/syncope	1. Yes	1. Mild
Standard balloon	Fall/syncope	1. Yes	1. Mild
Standard balloon	Fall/syncope	1. Yes	3. Severe
Standard balloon	Musculoskeletal	1. Yes	2. Moderate
Standard balloon	Musculoskeletal	1. Yes	3. Severe
Standard balloon	Musculoskeletal	1. Yes	3. Severe
Standard balloon	Hypertension	0. No	1. Mild
Standard balloon	Hypertension	0. No	1. Mild
Standard balloon	Hypertension	0. No	1. Mild
Standard balloon	Hypertension	1. Yes	1. Mild
Standard balloon	Hypertension	1. Yes	2. Moderate
Standard balloon	Bacteraemia	1. Yes	2. Moderate
Standard balloon	Bacteraemia	1. Yes	2. Moderate
Standard balloon	Bacteraemia	1. Yes	2. Moderate
Standard balloon	Cutaneous	0. No	1. Mild
Standard balloon	Cutaneous	1. Yes	3. Severe
Standard balloon	Neurological	1. Yes	3. Severe
Standard balloon	Neurological	1. Yes	3. Severe
Standard balloon	Other	0. No	3. Severe
Standard balloon	Other	1. Yes	1. Mild
Standard balloon	Other	1. Yes	2. Moderate
Standard balloon	Other	1. Yes	2. Moderate
Standard balloon	Other	1. Yes	3. Severe
Standard balloon	Other	1. Yes	3. Severe
Standard balloon	Other	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe
Standard balloon	Death	1. Yes	3. Severe

Section S7 Protocols and statistical analysis plans:

Original protocol (version 2.0, approved before the first site opened)

Final protocol (version 9.0)

Version control document (summary of changes)

Original statistical analysis plan (version 1.0)

Second and final statistical analysis plan (version 2.0, changes listed in section 1.6)

PROTOCOL TITLE

Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access (PAVE); A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel-assisted balloon angioplasty of venous stenoses in haemodialysis access

Trial Identifiers ISRCTN – REC Number – 15/LO/0638

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Study Synopsis

Title	**P**aclitaxel assisted balloon **A**ngioplasty of **V**enous stenosis in ha**E**modialysis access.
Protocol Short Title	PAVE Trial
Protocol Version number/ Date	Version 1.0
Is the study a Pilot?	No
Study Hypothesis	The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.
Methodology	Double-blind multicentre randomised controlled trial
Sponsor name	King's College London / GSTT NHS Foundation Trust
Chief Investigator	Dr Michael Robson
REC number	15/LO/0638
Condition under investigation	Arteriovenous fistulae used for haemodialysis in patients with end stage kidney disease.
Purpose of clinical trial	RCT to assess the efficacy of additional paclitaxel-coated balloon fistuloplasty compared to plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.
Number of Patients	211
Trial Design	Double-blind multicentre randomised controlled trial with variable follow up (minimum 1 year)
Endpoints	The primary endpoint is time to end of target lesion primary patency (TLPP). Secondary endpoints: 1. Angiographically determined late lumen loss 2. The rate of binary angiographic re-stenosis 3. Time to end of access circuit primary patency 4. Time to end of access circuit cumulative patency 5. Procedural success 6. Number of thrombosis events 7. Adverse events 8. Patient quality of life assessed by EQ-5D and POS-S Renal
Inclusion Criteria	1. Patients (18 years or over) who have a native AVF in the arm that has been used for haemodialysis for at least 12 dialysis sessions 2. An indication for a fistuloplasty as determined by the local clinical team 3. The access circuit is free of synthetic graft material or stents 4. A reduction of vessel diameter of ≥ 50% measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon 5. A residual stenosis of ≤ 30% after plain balloon fistuloplasty
Exclusion Criteria	1. Patient unable to give informed consent 2. Patient unwilling or unable to comply with all study-related procedures 3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure 4. Synchronous venous lesion (with a reduction of vessel diameter of ≥ 50% measured angiographically) in the same access circuit 5. Location of stenosis beyond the thoracic inlet 6. Thrombosed (failed) dialysis circuit at time of treatment 7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children within two years of study treatment 8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated 9. Known hypersensitivity or contraindication to paclitaxel
Statistical Methodology and Analysis	To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis.

Device Name	Lutonix 035 Drug Coated Balloon PTA Catheter (Treatment) Ultraverse 035 PTA Dilatation Catheter (Placebo) Dorado PTA Dilatation Catheter (Plain balloon)
Manufacturer Name	C.R Bard, Inc.
Principle intended use	Angioplasty of stenosed blood vessels
Is the device CE-marked and used within its purpose?	Yes
Is the device currently used within the department?	Yes

Description and Maintenance and storage of device
The balloons will be stored under routine conditions in the radiology department.
No special measures or maintenance is needed.

Are the devices registered on the DoH MIA Master Indemnity Scheme?	Yes

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
Atm	Atmospheres (pressure)
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
ISRCTN	International Standard Randomised Controlled Trial Number
REC	Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TLPP	Target Lesion primary patency
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Introduction

1.1. Existing research

Vascular access for haemodialysis
The 2012 UK Renal Registry report (www.renalreg.com) found that 43.9% of patients with end-stage kidney disease in the UK are on haemodialysis. This equated to 365 patients per million population in the UK in 2011. This number has increased every year with an overall increase of 3.6% from 2006 to 2011. In order to perform haemodialysis, reliable vascular access is essential. It is universally agreed that the optimal form of access is a native arteriovenous fistula (AVF). Although these are superior to synthetic arteriovenous grafts (AVGs), both AVFs and AVGs have a limited lifespan. Data from the Dialysis Outcomes and Practice Study (DOPPS) showed that in the US the one year patency for AVFs and AVGs is 68% and 49% respectively [1]. In Europe, one-year AVF survival was somewhat better at 83% but there is still a need for improvement.

Problems with vascular access are an important cause of morbidity and mortality in haemodialysis patients. In the US, it has been estimated that $1bn per year is spent on vascular access and its complications [2]. A recent survey in the UK found that haemodialysis patients occupy 320,000 bed days per year, with 30% of admissions related to vascular access (Renal Association vascular access audit, available at www.renal.org). Haemodialysis patients are at a greatly increased risk of invasive MRSA infection and this is largely related to the use of central venous catheters instead of AVFs or AVGs. When thrombosis or stenosis occurs in an AVF or AVG, a central venous catheter may be used for several months until an AVF or AVG is formed and is usable. In some patients, a central venous catheter may become the only dialysis access that can be used. Data from the US showed that the risk of invasive infection is increased 100 fold over the general population in haemodialysis patients, with 85% having catheters of invasive devices, and 90% requiring hospitalisation with a 17% mortality [3]. It is therefore imperative to preserve each AVF or AVG for as long as possible and to avoid the use of central venous catheters which lead to infective complications.

The initial therapy for a stenosis in an AVF is radiological balloon dilatation or angioplasty. Monitoring of AVFs for reduced blood flow and pre-emptive angioplasty, or surgery, is performed in some centres. Limited evidence supports this approach [4-6]. In contrast, the need for intervention when AVFs are clinically dysfunctional, with angioplasty or surgery, is established and will improve fistula function. A major concern however is the longevity of this effect. One recent study addressed this and documented the outcomes after angioplasty in 159 AVFs. Angioplasty was performed due to AVF dysfunction in 96% of cases. Primary assisted patency (AVF working regardless of repeat intervention) was 89% and 85% at 6 and 12 months respectively. However at 6, 12 and 24 months, the primary unassisted patency (AVF working with no repeat intervention) was 61%, 42% and 35% respectively [7]. These results are similar to our own local audit data, which showed 53% and 33% primary unassisted patency rate at 6 and 12 months respectively. It is also similar, as regards event rate, to the prospective study of Tessitore et al (5). In this study the primary outcome was AVF patency following angioplasty regardless of repeat intervention. However, the restenosis rate following the initial angioplasty was reported to be 39% per year, with a median time to this event of 8 months. In addition to the need for better interventions to reduce restenosis rates, there is also a need to better understand and identify the different types of response that occur following intervention.

The biology of arteriovenous fistula dysfunction

Neointimal hyperplasia leads to stenoses in the venous segments of AVFs, with the pathology characterised by an expansion of alpha smooth muscle actin positive myofibroblasts in the neointima [8]. In arteries, the contribution of bone-marrow derived cells to tissue repair depends on the nature and severity of injury [9]. The contribution of bone marrow cells to venous neointimal hyperplasia is not resolved and the data from animal studies are conflicting. Two studies using bone marrow transplantation with cells containing a green fluorescent protein (GFP) or β-galactosidase reporter gene, have suggested a minimal contribution of bone-marrow derived cells in mouse and rat model respectively [10, 11]. However a further study employing a murine vein graft, has suggested that at least 20% of neointimal cells may be bone marrow derived [12]. GFP positive cells were detected by a more sensitive PCR method and these technical differences were suggested as a reason for discrepancies with other studies.

In addition to these conflicting data on the origin of neointimal cells, it should be noted that none of the previous reports induced vein injury in way that would mirror the changes induced by angioplasty. Instead, most have focussed on the development of primary stenosis in venous grafts undergoing arterialisation, in which endothelium is 'traumatised' or activated by changes in the flow characteristics of arterial blood to which it becomes exposed. Given the data from arterial studies, a contribution from bone marrow cells to the alpha smooth muscle actin producing cells in the hyperplastic neointima of a dysfunctional AV fistula is highly likely with the degree of trauma to the endothelium that would follow angioplasty. Angioplasty causes vessel wall damage with rupture of the junction between the intima and the media, with a burst of proliferation and repair. Much of our understanding of aggressive neointimal formation in this context comes from arterial studies [13], but similar pathology and an increase in proliferation has been shown in AVFs following venous angioplasty [14].

Paclitaxel exerts an antiproliferative effect by interfering with cell microtubule function [15]. Systemic administration of paclitaxel after angioplasty in the rat carotid artery showed that a significant reduction in neointimal proliferation could be achieved at doses much lower than antineoplastic levels [16]. In rat and human cultured cell models, paclitaxel inhibited vascular smooth muscle cell migration and proliferation [16, 17], consistent with its effects in vivo. As an alternative to systemic therapy, local drug delivery offers the advantages of allowing high local concentrations of drug at the treatment site while minimising systemic toxic effects. Proof of this possibility was initially shown using paclitaxel-coated stents in pig coronary arteries [18].

Recent advances in technology have allowed angioplasty balloons to be coated with paclitaxel. This allows local delivery of paclitaxel to the site of stenosis. A number of multi-centre randomised controlled trials in the coronary and peripheral arterial circulation have established the positive benefit of drug-coated balloons [19, 20]. A small pilot study has suggested efficacy in dialysis patients [21]. In this study, 40 patients with AVFs or AVGs were randomised to paclitaxel for the treatment of a clinically important stenosis. Unassisted primary patency of the treated lesion (defined angiographically as a binary readout of <50% stenosis) at 6 months was significantly better in the paclitaxel-coated balloon group (70 v 25%). This study may be criticised on a number of points. These include the use of an angiographic rather than a clinical endpoint, the lack of blinding and independent angiographic core lab analysis, the very small sample size originally intended to test non-inferiority only (with a wide 15% non-inferiority limit), and the short 6-month follow-up. In addition, a range of balloons was used in the control group for post-dilation after the paclitaxel-coated balloons, and these were not universally high pressure and non-compliant. This may have added variability to the outcome. Furthermore, the inclusion of both AVFs (35%) and AVGs (65%) may have resulted in significant confounding, given the difference in survival rates associated to the two types of access. Despite these

limitations, the results suggested that a further study of efficacy was warranted, which is what we propose here. This is the first large scale randomised controlled trial designed to test superiority of drug-coated balloons in haemodialysis access circuits.

1.2. Risks and benefits

The risks for patients taking part in this study are minimal. The plain balloon fistuloplasty is standard of care and the additional intervention will be the use of a paclitaxel-coated balloon or control balloon following this initial dilatation. The paclitaxel-coated balloons that will be used are CE marked and there have been no safety concerns with their use. In the specific context of haemodialysis AVFs, the pilot study performed did not raise any safety concerns [21].

1.3. Rationale for current study:

The overriding aim of this study is preservation of vascular access for haemodialysis with a reduction in restenosis and the need for repeat fistuloplasties.

Clinical Trial

Our hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic AVFs. As detailed in section 1.1, this hypothesis is supported by what is known of the effects of paclitaxel on the biology of neointimal formation, results in trials involving coronary and peripheral arteries, and a pilot study vascular access for haemodialysis.

This need for repeat procedures following angioplasty is expensive and inconvenient for patients and is needed in around 60% of patients during the first year [7]. As detailed in our sample size calculation we predict that the use of paclitaxel coated balloons will lead to an avoidance of the need for repeat angioplasty. Repeat angioplasties will also have a negative effect on patient quality of life and a reduction in these will be a benefit in addition to the reduction in cost.

Collection of patient samples

This clinical trial offers a unique opportunity to collect patient samples alongside detailed and carefully collected clinical and angiographic data in the setting of a clinical trial. This will form an important resource for future laboratory based studies on biomarkers and AVF outcomes.

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2. Trial Objectives, Design and Statistics

2.1. Trial objectives

The purpose of this RCT is to assess the efficacy of additional paclitaxel-coated balloon fistuloplasty compared to plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

Primary Endpoint:

Time to end of target lesion primary patency

This is defined as patency with no re-intervention to the area 5mm proximal within, and 5 mm distal to, the index treatment segment. Target lesion primary patency ends when *any* of the following occur: (a) re-intervention to the treatment segment; (b) thrombotic occlusion that includes the treatment segment; (c) surgical intervention that excludes the treatment segment from the access circuit; (d) abandonment of the AVF due to an inability to retreat the treatment segment.

Referral for a repeat procedure will originate from the clinical team who are unaware of whether the patient received treatment with a paclitaxel-coated balloon or uncoated control balloon.

In order to confirm there is a significant stenosis prior to fistulography, a duplex ultrasound is encouraged but is not mandatory.

A different radiologist to the one performing the index procedure will perform repeat procedures when possible but it is not possible to guarantee this. Therefore the radiologist performing the repeat procedure may have knowledge of whether the patient was treated with drug-coated balloon or placebo.

In order to allow us to demonstrate that there is no bias in the final decision to proceed with the repeat intervention we will do the following: In patients *who have not yet reached the primary endpoint,* any pre-procedure fistulograms prior to re-intervention or potential re-intervention will be sent to an independent angiographic laboratory for analysis. This will allow confirmation that a significant stenosis was found in all patients who received a repeat intervention, and not in the small number who underwent fistulography but not an intervention, regardless of which arm of the trial the patient is in. The specifications for this fistulogram are defined in section 4.5.

Secondary Endpoints:

1. Angiographically determined late lumen loss.

This is the difference between the diameter of the treatment segment post-procedure and the diameter at 6 months as measured by an independent core laboratory. If a patient has a repeat procedure to the treatment segment before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.

2. The rate of angiographic binary re-stenosis.

This is defined as the incidence of stenosis of at least 50% within the treated lesion at the 6 month follow-up fistulogram. If a patient has a repeat procedure to the index lesion before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.

3. Time to end of access circuit primary patency

The access circuit is defined as starting at the arterial anastomosis and ending at the cavoatrial junction. Access circuit primary patency ends when *any* of the following occur: (a) access circuit thrombosis, (b) an intervention (either radiological or surgical) anywhere in the access circuit, or (c) the access circuit is abandoned due to an inability to treat any lesion.

4. Time to end of access circuit cumulative patency

Access circuit cumulative patency ends when the AVF is abandoned, regardless of radiological or surgical intervention, with or without a thrombosis event. Multiple/repetitive treatments for stenoses that restore patency are compatible with cumulative patency.

5. Procedural success (residual stenosis ≤ 30% on completion fistulogram II, see section 4.4 below)

6. Number of thrombosis events

7. Adverse events (e.g. fistula rupture, infection)

8. Patient quality of life as assessed by the EuroQuol EQ-5D generic health survey, and the disease specific Patient (or Palliative care) Outcome Scale symptom score-renal (POS-S Renal) [22].

2.2 Trial design

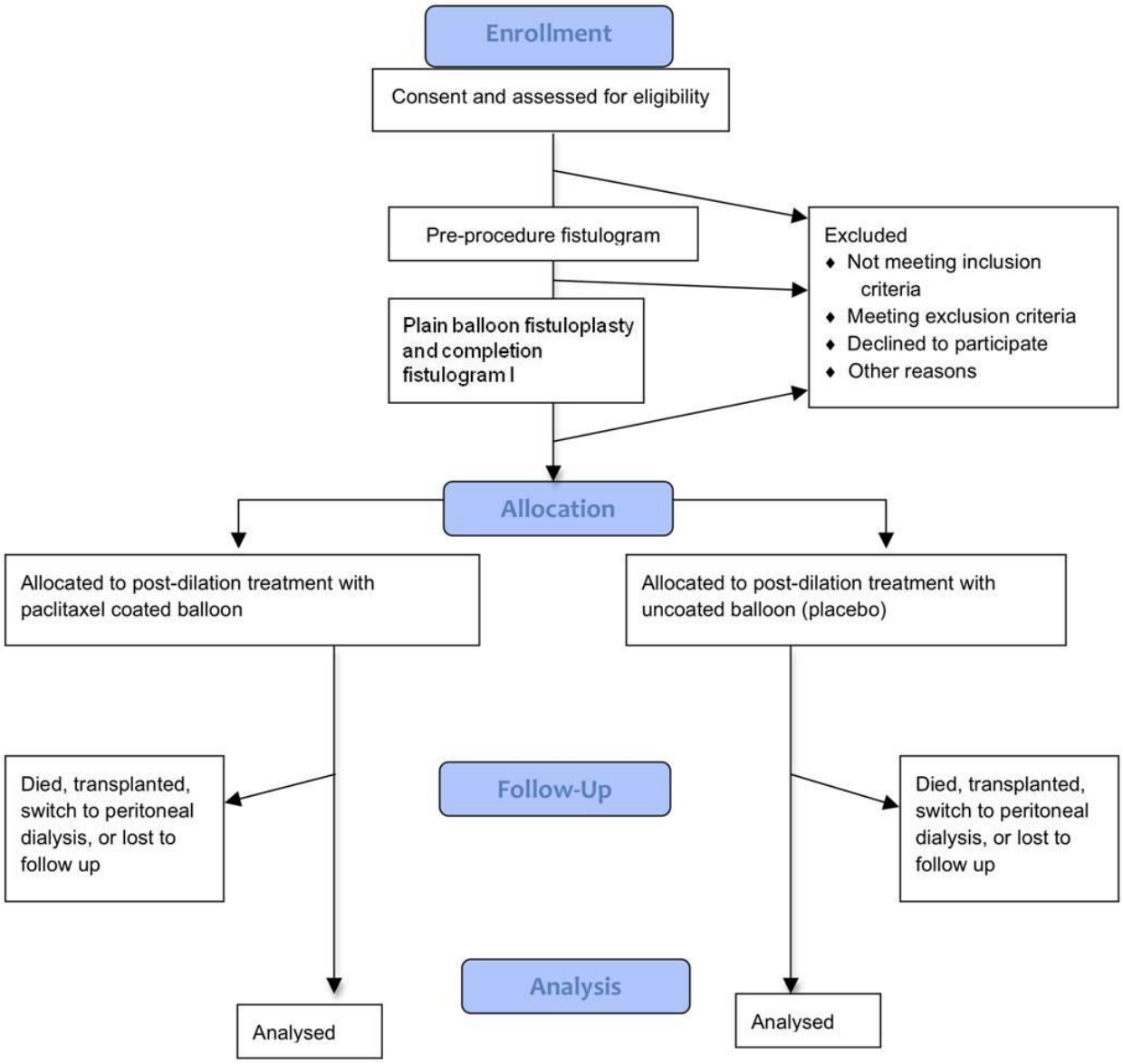
The study design used to achieve this will be a double-blind multicentre randomised controlled trial. We will recruit 211 patients over a two-year period. Patients will be randomized in a 1:1 ratio. Randomisation will be stratified for two variables. These will be firstly study centre and secondly, whether they have had a previous radiological intervention to the treatment area or not. Patients will be followed up for a minimum of one year, and all patients will continue in the study until the last patient has completed one year of follow up.

2.3 Trial schedule

	Pre-procedure	Procedure						Post-procedure ****												
								Day 1-3	mth 3	mth 6	mth 9	mth 12	mth 15	mth 18	mth 21	mth 24	mth 27	mth 30	mth 33	mth 36
Patient registration and consent	x																			
Medical history (including indication for fistuloplasty)	x																			
Consideration of eligibility	x																			
Discussion and confirmation of potential eligibility with radiologist	x																			
Blood samples (taken on dialysis when possible)	x							x	x	x										
Pre-procedure fistulogram *		x																		
Plain balloon fistuloplasty			x																	
Completion fistulogram I *				x																
Randomisation					x															
Study treatment						x														
Completion fistulogram II							x													
Protocol fistulogram										x										
Follow up assessments ** ***									x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments (POS-S Renal and EQ-5D)	x									x		x								

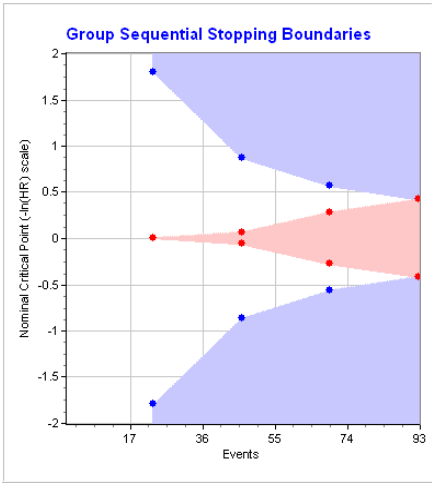
* Prior to randomisation, eligibility will be reviewed based on the radiological findings on both the pre-procedure fistulogram and completion fistulogram I
**At each follow up assessment information to be checked or collected will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, thrombosis events, patient medications, access circuit dysfunction, and adverse events.
***Follow up will be for a minimum of 12 months and a maximum of 36 months.
****Post-procedure study assessments occur every 3 months ± 1 month.

2.4 Trial flowchart



2.5 Trial statistics

Analysis of Primary Outcome: To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis. Primary analysis will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates. Patients with TLPP at the end of follow up will be considered censored, as will those who receive a renal transplant, switch to peritoneal dialysis or are lost to follow up before the study end. Kaplan-Meier plots, hazard-ratio and its confidence interval will be used to describe the results.



Analysis of Secondary Outcomes: Effects on secondary outcomes will be analysed using the same strategy for time-to-event variables, and generalized linear models for binary and continuous outcome measures, adjusting for the effects of relevant covariates when appropriate. Continuous variables will be checked for normality, transformed if necessary or otherwise analysed using a Wilcoxon-signed-rank test for independent samples.

Missing Values and Drop-outs: If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. Patients lost to follow up will be compared to patients who reach complete follow up in baseline characteristics and adverse events to test whether drop-outs are random.

Interim Analysis: Interim analysis of the primary outcome will be performed three times throughout the study, based on the cumulative number of failures of the treatment area, i.e. after 27, 54 and 81 events, expected approximately at 9, 14 and 19 months of study under the null, and at months 11, 17, and 23 under the alternative. Group sequential stopping boundaries have been calculated using a Lan-de-Mets spending function (with O'Brian-Fleming parameters), to allow early stopping for rejection of the null or the alternative hypotheses. Stopping in case of boundary crossing is non-binding.

3. Sample Size, Selection and Withdrawal of Subjects

3.1 Sample size

For the definition of the survival curve in the placebo balloon group, we assumed target lesion primary patency of 61%, 42%, and 35% at 6, 12 and 24 months respectively. This was consistent with published results [7] and with our own audit data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect size. Katsanos et al. [21] found a HR of 0.3 for TLPP at 6 months; however, the confidence interval was broad and the effect size is expected to be closer to the null when AVGs are excluded. Based on these assumptions, it is expected that the paclitaxel coated balloon group will show 78%, 65%, and 59% survival of TLPP at 6, 12 and 24 months respectively. Recruiting 211 patients, with variable follow up, a minimum follow up of 1 year, and three interim analyses, will provide 94% power to detect a statistically significant difference between the two groups in TLPP survival with 2-sided 5% type I error rate. It is expected that 108 patients will experience fistula failure during the follow up period.

The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, and recruitment of 2 patients per month (ppm) during the first three months, 8 ppm up to 7 months, and 12 ppm onwards. The expected accrual duration will be 22 months, and the maximum study duration (including follow-up) 34 months.

3.2 Inclusion criteria

1. Patients (18 years or over) who have a native AVF in the arm that has been used for haemodialysis for at least 12 dialysis sessions.

2. An indication for a fistuloplasty as determined by the local clinical team

3. The access circuit is free of synthetic graft material or stents

4. A reduction of vessel diameter of ≥ 50% measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon

5. A residual stenosis ≤ 30% after plain balloon fistuloplasty

3.3 Exclusion criteria

1. Patient unable to give informed consent

2. Patient unwilling or unable to comply with all study-related procedures

3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure

4. Synchronous venous lesion, with a reduction of vessel diameter of ≥ 50% measured angiographically, in the same access circuit

5. Location of stenosis beyond the thoracic inlet

6. Thrombosed (failed) dialysis circuit at time of treatment

7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children, within two years of study treatment

8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated

9. Known hypersensitivity or contraindication to paclitaxel

3.4 Criteria for premature withdrawal

Participants have the right to withdraw from the study at any time for any reason.

Participants will be withdrawn from the study if any of the following occur:

- Death of participant
- Participant receives a transplant
- Participant is changed from haemodialysis to peritoneal dialysis

The PI also has the right to withdraw patients from the study in the event of inter-current illness, AEs, SAE's, protocol violations, administrative reasons or other reasons, e.g. the participant is no longer being treated at a hospital included in the study.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Participants who wish to withdraw from 'treatment' will be asked to confirm whether they are still willing to provide study specific data and samples for scientific laboratory analysis according to the trial protocol.

4. Study Procedures

4.1 Screening procedures

Patients that may be eligible will be identified in a vascular access clinic and assessed by surgeons, specialist nurses and nephrologists.

In order to confirm there is a significant stenosis prior to angiography, a duplex ultrasound is encouraged but is not mandatory.

At least 24 hours after being given the patient information sheet and before entering the angiography room for the pre-procedure fistulogram, consent will be taken and eligibility criteria as listed above in section 3 will be assessed. Inclusion criteria 1 and 2 will be confirmed and exclusion criteria 1-3 and 6-9 will be assessed.

The radiologist who will perform the pre-procedure fistulogram will be informed that the patient is potentially eligible for the study.

4.2 The pre-procedure fistulogram

This will be performed in a dedicated Interventional Radiology suite equipped with digital subtraction angiogram, image overlay/roadmap post processing capabilities and ability to capture still and video DICOM file data.

This will be take place immediately prior to the plain balloon fistuloplasty.

It will be performed through a sheath or cannula placed in the dialysis circuit according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
2. The entire access circuit from anastamosis to central vein covered in up to 3 stages
3. Medial epicondyle of humerus visible bony landmark on lower arm acquisition, acromioclavicular joint on upper arm and central acquisitions
4. Measurement ruler in view
5. Lower arm acquisition to include:
    i. Anteroposterior Projection of anastomosis
    ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)
6. On the acquisition that best demonstrates the target lesion, the following measurements are made:
    i. Proximal (close to anastomosis) reference vessel diameter
    ii. Minimum lumen diameter (MLD)
    iii. Distal reference vessel diameter

The radiologist will assess inclusion criteria 3 and 4, and exclusion criteria 4 and 5, to decide if the patient remains eligible for the study.

4.3 The plain balloon fistuloplasty procedure

This will be performed in a dedicated Interventional Radiology suite equipped with digital subtraction angiogram, image overlay/roadmap post processing capabilities and ability to capture still and video DICOM file data, according to the following specifications:

Prior to treatment 3000-5000 IU of heparin is administered. For all patients treatment has two components. The first is fistuloplasty, performed with a dedicated high pressure balloon (*Bard Dorado*) ensuring the following criteria are met:

1. Sized to nominal vein diameter
2. Up to 24 Atm to ensure obliteration of the lesion waist
3. Minimum duration of balloon inflation 1 minute.

If further plain balloon fistuloplasty treatment is required, then this may be administered once more only.

Completion fistulogram I is performed after the plain balloon fistuloplasty to ensure adequate therapy according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
2. Acquisition that demonstrates the target lesion matched as close as possible to the respective pre-procedure fistulogram acquisition
3. Measurement ruler in view
4. The following measurements are made:
    i. Proximal (close to anastomosis) reference vessel diameter
    ii. Minimum lumen diameter (MLD)
    iii. Distal reference vessel diameter

The radiologist will assess completion fistulogram I and decide if the residual stenosis is ≤ 30% (inclusion criteria 5). If this is the case the patient will proceed to randomisation, but if not the patient will be excluded.

4.4 Randomisation procedures

Randomisation will take place via a web based randomisation service, hosted at the UKCRC registered clinical trials unit at KCL. Site staff will access the service via www.ctu.co.uk using a computer in the angiography room or an office nearby. It will be performed by the radiologist or their nominee. Each randomiser will have unique user access. Access will be provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed and relevant documentation regarding the individuals has been collected. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention.

Patients will be randomized in a 1:1 ratio. The two groups will be stratified by two variables. These will be firstly study centre and secondly, whether they have had a previous radiological intervention to the treatment area or not. Once randomised, email confirmations will be generated from the randomisation system and will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study.
If it is not possible to use the randomisation system randomisation may occur using the toss of a coin in order to avoid losing the patient from the study. *This should only be needed, if at all, in specific and rare situations such as the CTU server being inaccessible.* This will be performed by two people with heads denoting drug-coated balloon, and tails denoting placebo. The CTU must be informed of the coin randomisation as soon as possible.

4.5 Study treatment

In the intervention arm, the second component is insertion of a drug coated balloon (*Bard Lutonix*) of identical diameter and length to the high pressure balloon inflated to nominal pressure at the lesion location for a minimum of 1 minute duration.

Instructions for use of the drug coated balloon are stringently adhered to ensure appropriate preparation and handling of the device.

In the control arm, an identical procedure is followed, but using a placebo balloon that is not drug coated (*Bard Ultraverse)*, of identical diameter and length to the high pressure balloon inflated to nominal pressure at the lesion location for a minimum of 1 minute duration.

In both arms, image overlay/roadmap will be utilized to ensure that there is no geographical mismatch between the segments treated with the high and low pressure balloons.

Only the above 3 balloon types (*Bard Dorado, Bard Lutonix and Bard Ultraverse*) may be used in the study to ensure consistency and the above fistuloplasty procedure must be exactly followed.

A completion fistulogram is again performed (completion fistulogram II) to confirm no angiographically visible effect after treatment with the drug-coated or placebo balloon, according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
2. Acquisition that demonstrates the target lesion matched as close as possible to the respective pre-procedure fistulogram acquisition
3. Measurement ruler in view
4. The following measurements are made:
    i. Proximal (close to anastomosis) reference vessel diameter
    ii. Minimum lumen diameter (MLD)
    iii. Distal reference vessel diameter

Procedural success is defined as a residual stenosis ≤ 30% on completion fistulogram II.

The data file(s) containing the initial pre-procedure fistulogram, and completion fistulogram I and II will be sent to the lead study site with the patient's name replaced by the trial ID, and with each of the above groups of images clearly identified. Completion fistulogram II will then be sent to the independent angiographic laboratory for analysis.

4.6 Study assessments

These will occur every 3 months ± 1 month. Follow up will be variable but for a minimum of 1 year and a maximum of 3 years. These will involve a clinical assessment to take place either face-to-face or via a telephone conversation. Any face-to-face meetings will usually coincide with dialysis to avoid additional patient travel.

Data recorded for each study assessment will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, thrombosis events, patient medications, access circuit dysfunction, and adverse events. At the 6 month study assessment, the trial team will check if referral for re-intervention is being considered based on clinical concerns. If this is the case then a fistulogram ±plasty will be performed according to usual clinical practice and the patient will not undergo a protocol fistulogram.

If there are no clinical concerns related to the fistula, then patients will be invited to undergo a protocol fistulogram. Confirmation that there is no contraindication to this protocol fistulogram will be obtained from an appropriate doctor and documented.

4.7 Radiology Assessments

4.7.1 The 6 month protocol fistulogram

This will take place within 2 weeks of the 6 month study assessment.

If a patient has required a repeat fistuloplasty to the treatment area at or before 6 months then they will not undergo the 6 month protocol fistulogram.

All other patients will be invited to undergo a protocol fistulogram 6 months after the index procedure to acquire the data for the angiographic secondary endpoints 1 and 2 above. If a patient declines the 6 month protocol fistulogram of does not have it for another reason, this will not be considered a protocol violation and the patient may continue in the study.

The 6 month protocol fistulogram *must* be performed by a radiologist other than the one who performed the index procedure to ensure that they are blind to which trial arm the participant belongs. With forward planning this should be possible but if it is not then the protocol fistulogram should not be performed.

A fistuloplasty will not be performed at the time of the 6 month protocol fistulogram unless an unsuspected stenosis is found and the radiologist believes that it would be unethical not to intervene. This will not be considered a protocol violation and a fistula intervention form must be completed.

The 6 month protocol fistulogram will be performed in a dedicated Interventional Radiology suite equipped with digital subtraction angiogram, image overlay/roadmap post processing capabilities and ability to capture still and video DICOM file data. It will be performed through a sheath or cannula placed in the dialysis circuit according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second

2. The entire access circuit from anastomosis to central veins covered in up to 3 stages

3. Medial epicondyle of humerus visible bony landmark on lower arm acquisition, acromioclavicular joint on upper arm and central acquisitions

4. Measurement ruler in view

5. Lower arm acquisition to include:
   i. Anteroposterior Projection of anastomosis
   ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)

6. On the acquisition that best demonstrates the target lesion, the following measurements are made:
   i. Proximal (close to anastomosis) reference vessel diameter
   ii. Minimum lumen diameter (MLD)
   iii. Distal reference vessel diameter

The 6 month protocol fistulogram will be considered to be exclusively trial data. The result of the 6 month protocol fistulogram will not be made available (verbally or in writing) to the clinical team responsible for considering future referral of the patient to radiology. The images will also not be available on the local radiology system. The images will be sent to the lead site in order to be forwarded to the independent core laboratory with the patient's name replaced by the trial ID.

4.7.2 Fistulograms performed for a clinical indication

The follow applies only in patients who have not yet reached the primary endpoint of the trial.

Pre-procedure fistulograms performed for a clinical indication will follow these specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
2. The entire access circuit from anastomosis to central veins covered in up to 3 stages
3. Medial epicondyle of humerus visible bony landmark on lower arm acquisition, acromioclavicular joint on upper arm and central acquisitions
4. Measurement ruler in view
5. Lower arm acquisition to include:
    i. Anteroposterior Projection of anastomosis
    ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)
6. On the acquisition that best demonstrates the target lesion, the following measurements are made:
    i. Proximal (close to anastomosis) reference vessel diameter
    ii. Minimum lumen diameter (MLD)
    iii. Distal reference vessel diameter

The image file will be sent to the lead site in order to be forwarded to the independent core laboratory for analysis with the patient details replaced by the trial PIN. This will be sent regardless of whether the fistulogram is followed by a fistuloplasty.

This will allow us to demonstrate that there is no bias in the final decision to proceed, or not, with the repeat intervention.

4.8 End of Study Definition

The clinical trial will end when 211 patients have been recruited and all patients have completed at least one year of follow up.

The trial may be prematurely discontinued by the Sponsor, Funder, Chief Investigator or TSC on the basis of new safety information or for other reasons given by the DMC, TSC, REC, or from other sources. The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected.

5. Laboratories

5.1 Laboratory tests

There are no local laboratory tests that are required to provide data that directly relate to trial endpoints. A 10 ml blood sample will be requested at the four timepoints stated in the trial schedule (2.3), and is to be sent to the local clinical laboratory for a full blood count and to check the C-reactive protein level. If patients decline some or all of these samples it will not be considered a protocol violation.

5.2 Core laboratory angiographic analysis

The completion fistulogram II (taken after treatment with the drug coated balloon or placebo low pressure balloon) will be analysed in a core laboratory and compared with the pre-procedure

fistulogram performed routinely at 6 months (or the pre-procedure fistulogram taken prior to any re-intervention at the treatment area if this is before 6 months).

In addition, any pre-procedure fistulograms that are not followed by a re-intervention, and any pre-procedure fistulograms that are performed after 6 months and are followed by a re-intervention, will be sent to the core laboratory for analysis. This is to allow an objective assessment of the decision to intervene or not after the pre-procedure fistulogram.

5.3 Research sample Collection

Blood (up to 90 ml) may be taken at each of the time points in the table of events in 2.3. These will be sent to the research laboratory of the CI where the blood will be separated. Research blood samples should not be taken from patients who are known to be hepatitis B sAg, hepatitis C IgG or RNA, or HIV positive.

DNA and RNA will be stored. Cells will be stored in aliquots in liquid nitrogen until thawed for analysis. Serum and/or plasma samples will be stored at -20'C or -80'C until thawed for analysis. Transport, separation and storage will be according to Standard Operating Procedures.

It will not be a considered a protocol violation if any of the blood samples are not taken, or are taken at different time points to those specified and patients may continue on the study.

6. Assessment of Safety

We have been informed by the MHRA that the PAVE protocol does not fall within the Clinical Trial Regulations and therefore is not a drug trial. In addition, the drug-coated balloon is a CE-marked medical device, so prior regulatory approval from the MHRA is not needed.

Safety reporting will be in keeping with the requirements for research other than Clinical Trials of Investigational Medicinal Products.

A Serious Adverse Event (SAE) is an untoward occurrence that:

a) results in death
b) is life-threatening
c) requires non-elective hospitalisation or prolongation of existing hospitalisation
d) results in persistent or significant disability or incapacity
e) consists of a congenital anomaly or birth defect
f) is otherwise considered medically significant by the investigator.

All SAEs will be reported by the local investigators on the SAE form to the Chief Investigator, immediately they become aware and within 24 hours at most. A planned or non-elective hospital admission does not need to be reported as an SAE unless the PI decides it should be.

Although it is not an SAE, any pregnancy or fathering of children that occurs within 2 years of the study treatment will be reported via the SAE system as below.

Reports of SAEs will be reviewed by the CI within 24 hours to assess whether the event is related to the research procedure and unexpected (a SUSAR) and if so, it will be onward reported to the REC and DMC within 15 days, in the format prescribed by NRES and published on the website.

Since the study treatment is local and not systemic, non-serious adverse events will be defined as events that the PI considers are directly related to the vascular access that has been treated. These should be recorded throughout the trial and will be captured in the eCRF at each study assessment.

7. Data Monitoring Committee

The membership will be decided by the CI and approved by the NIHR. The DMC includes a statistician and two other independent experts. They will receive a report of recruitment, serious and non-serious adverse events and a summary of accumulated clinical data from the trial statistician, and will meet in person or by telephone. They will report to the TSC who will usually meet in the two weeks following the DMC meeting. The DMC will meet at least annually during the study, approximately 2 weeks prior to the TSC. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The DMC is advisory to the TSC. The DMC charter will be drafted and agreed prior to recruitment. The Trial Statistician will prepare reports to the DMC.

8. Trial Steering Committee

The TSC will be convened in the post-award period. The membership will be decided by the CI and approved by the NIHR. The chair will be an independent expert. Members will include the CI, a patient representative, and two other independent experts. The TSC will meet at least annually during the study, approximately 2 weeks after the DMC. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The TSC is an executive committee. Terms of reference of the TSC will be agreed and documented prior to start of recruitment. The Trial Manager will prepare reports to the TSC.

9. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework.

This protocol and related documents will be submitted for review to the London-Chelsea Research Ethics Committee (REC).

The Chief Investigator will submit a final report at conclusion of the trial to the sponsor and the REC.

Annual progress reports will be submitted to the main REC for the study.

10. Data Handling

All samples will be anonymised before laboratory analysis. No patient-related data will be held in research laboratories.

During the study, any paper documents will be held in a locked filing cabinet in a locked office and retained for a minimum of 5 years following the end of the study.

Clinical and research data for the study will be stored on the eCRF system, hosted at the King's Clinical Trials Unit, KCL. The eCRF (InferMed MACRO) is GCP and FDA 21 CFR Part 11 compliant. Data entry staff at site will be provided with unique usernames and passwords to the system and will be trained in data entry by the trial manager. The trial manager will visit sites to review data on the system, raise discrepancies and confirm source data verification checks. All requests for access to the data entry system must be authorised by the trial manager. All requests for data exports must be authorised by the trial statistician. The trial manager will work with the CI and the trial statistician to ensure data is checked and cleaned on an ongoing basis and will confirm all data checks have been completed before database lock.

The investigators and the institutions will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other relevant documents (i.e. patients' case sheets, blood test reports, X-ray reports). Record keeping will be the responsibility of the investigators.

11. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The chief investigator will review all presentations and publications arising from this study and decide authorship in accordance with accepted guidelines.

12. Insurance / Indemnity

The study will be indemnified by King's College London for negligent and non-negligent harm. In addition, the recruiting sites will have NHS indemnity.

13. Financial Aspects

The NIHR have supported the study through an EME programme grant award. The fistuloplasty balloons are supplied by C.R. Bard, Inc. who have no other role in the design, running or analysis of the trial.

PROTOCOL TITLE

Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access (PAVE); A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel-assisted balloon angioplasty of venous stenoses in haemodialysis access

Trial Identifiers ISRCTN – 14284759 REC Number – 15/LO/0638

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Study Synopsis

Title	**P**aclitaxel assisted balloon **A**ngioplasty of **V**enous stenosis in ha**E**modialysis access.
Protocol Short Title	PAVE Trial
Protocol Version number/ Date	Version 9.0 08/11/2018
Is the study a Pilot?	No
Study Hypothesis	The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.
Methodology	Double-blind multicentre randomised controlled trial
Sponsor name	King's College London / GSTT NHS Foundation Trust
Chief Investigator	Dr Michael Robson
REC number	15/LO/0638
Condition under investigation	Arteriovenous fistulae used for haemodialysis in patients with end stage kidney disease.
Purpose of clinical trial	RCT to assess the efficacy of additional paclitaxel-coated balloon fistuloplasty compared to plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.
Number of Patients	211
Trial Design	Double-blind multicentre randomised controlled trial with variable follow up (minimum 1 year)
Endpoints	The primary endpoint is time to end of target lesion primary patency (TLPP). Secondary endpoints: 1. Angiographically determined late lumen loss 2. The rate of binary angiographic re-stenosis 3. Time to end of access circuit primary patency 4. Time to end of access circuit cumulative patency 5. Procedural success 6. Number of thrombosis events 7. Total number of interventions 8. Adverse events 9. Patient quality of life assessed by EQ-5D and POS-S Renal
Inclusion Criteria	1. Patients (18 years or over) who have a native AVF in the arm 2. An indication for a fistuloplasty as determined by the local clinical team 3. The access circuit is free of synthetic graft material or stents 4. A reduction of vessel diameter of ≥ 50% measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon 5. A residual stenosis of ≤ 30% after plain balloon fistuloplasty 6. A treatment segment, containing one or more lesions, which can be treated with ≤120 mm of a single drug-coated balloon
Exclusion Criteria	1. Patient unable to give informed consent 2. Patient unwilling or unable to comply with all study-related procedures 3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure. 4. One or more lesions outside the treatment segment, with a reduction of vessel diameter of ≥ 50% measured angiographically, in the same access circuit. The patient will also be excluded if any lesions outside the treatment segment are treated even if these are <50%. 5. Location of stenosis central to the thoracic inlet 6. Thrombosed (failed) access circuit at time of treatment 7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children within two years of study treatment

	8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated 9. Known hypersensitivity or contraindication to paclitaxel
Statistical Methodology and Analysis	To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis.

Device Name	Lutonix 035 Drug Coated Balloon PTA Catheter (Treatment) Ultraverse 035 PTA Dilatation Catheter (Placebo) Dorado PTA Dilatation Catheter (Plain balloon)
Manufacturer Name	C.R Bard, Inc.
Principle intended use	Angioplasty of stenosed blood vessels
Is the device CE-marked and used within its purpose?	Yes
Is the device currently used within the department?	Yes

Description and Maintenance and storage of device
The balloons will be stored under routine conditions in the radiology department.
No special measures or maintenance is needed.

Are the devices registered on the DoH MIA Master Indemnity Scheme?	Yes

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
Atm	Atmospheres (pressure)
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
ISRCTN	International Standard Randomised Controlled Trial Number
REC	Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
PTA	Percutaneous Transluminal Angioplasty
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
PCB	Paclitaxel-coated balloon
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

SSA	Site Specific Assessment
TLPP	Target Lesion primary patency
TMG	Trial Management Group
TSC	Trial Steering Committee

Disclaimer

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1. Introduction

1.1. Existing research

Vascular access for haemodialysis

The 2012 UK Renal Registry report (www.renalreg.com) found that 43.9% of patients with end-stage kidney disease in the UK are on haemodialysis. This equated to 365 patients per million population in the UK in 2011. This number has increased every year with an overall increase of 3.6% from 2006 to 2011. In order to perform haemodialysis, reliable vascular access is essential. It is universally agreed that the optimal form of access is a native arteriovenous fistula (AVF) are superior to synthetic arteriovenous grafts (AVGs) and tunnelled central venous catheters for haemodialysis access, AVFs and AVGs have limited lifespans. Data from the Dialysis Outcomes and Practice Study (DOPPS) showed that in the US the one year patency for AVFs and AVGs is 68% and 49% respectively. In Europe, one-year AVF survival was somewhat better at 83% but there is still a need for improvement [1]..

Problems with vascular access are an important cause of morbidity and mortality in haemodialysis patients. In the US, it has been estimated that $1bn per year is spent on vascular access and its complications [2]. A recent survey in the UK found that haemodialysis patients occupy 320,000 bed days per year, with 30% of admissions related to vascular access (Renal Association vascular access audit, available at www.renal.org). When thrombosis or stenosis occurs in an AVF or AVG, a central venous catheter may be used for several months until an AVF or AVG is formed and becomes usable. Data from the US has shown that the risk of invasive infection is increased 100 fold in haemodialysis patients compared to the general population. 85% of those diagnosed with an infection have an invasive device in situ. 90% of those diagnosed with an infection require hospitalisation and there is a 17% associated mortality [3]. It is therefore imperative to preserve each AVF or AVG for as long as possible and to minimise the use of central venous catheters.

The initial therapy for a stenosis in an AVF is radiological fistuloplasty. A major concern however is the longevity of this effect. Turmel-Rodrigues et al reported the outcomes of interventional salvage of dysfunctional and thrombosed haemodialysis circuits [4]. There were 220 cases in the dysfunctional AVF group. The 6, 12, 24 month primary patency (AVF working with no repeat intervention) reported were 67%, 51% and 37% for forearm AVF and 57%, 35% and 24% for upper arm AVF respectively. Bountouris et al. reported the outcomes after 159 percutaneous transluminal angioplasties (PTAs) in AVFs. The primary patency at 6, 12 and 24 months were 61%, 42% and 35% respectively [5]. Primary assisted patency (AVF working regardless of repeat intervention) was 89% and 85% at 6 and 12 months respectively. Although there have been some exceptions [6, 7], most other studies have reported similar primary patency rates of

around 40-50% at one year [8-10].

The biology of arteriovenous fistula dysfunction

In addition to the need for better interventions to reduce restenosis rates, there is also a need to better understand and identify the different types of response that occur following intervention. Neointimal hyperplasia leads to stenoses in the venous segments of AVFs, with the pathology characterised by an expansion of alpha smooth muscle actin positive myofibroblasts in the neointima [11]. In arteries, the contribution of bone-marrow derived cells to tissue repair depends on the nature and severity of injury [12]. The contribution of bone marrow cells to venous neointimal hyperplasia is not resolved and the data from animal studies are conflicting. Two studies using bone marrow transplantation with cells containing a green fluorescent protein (GFP) or β-galactosidase reporter gene, have suggested a minimal contribution of bone-marrow derived cells in mouse and rat model respectively [13, 14]. However a further study employing a murine vein graft, has suggested that at least 20% of neointimal cells may be bone marrow derived [15]. GFP positive cells were detected by a more sensitive PCR method and these technical differences were suggested as a reason for discrepancies with other studies.

In addition to these conflicting data on the origin of neointimal cells, it should be noted that none of the previous reports induced vein injury in a way that mirrors the changes induced by angioplasty. Instead, most have focussed on the development of primary stenosis in venous conduits undergoing arterialisation where endothelium is 'traumatised' or activated by changes in the flow characteristics of arterial blood to which it becomes exposed. Given the data from arterial studies, a contribution from bone marrow cells to the alpha smooth muscle actin producing cells in the hyperplastic neointima of a dysfunctional AV fistula is highly likely with the degree of trauma to the endothelium that would follow angioplasty. Angioplasty causes vessel wall damage with rupture of the junction between the intima and the media, with a burst of proliferation and repair. Much of our understanding of aggressive neointimal formation in this context comes from arterial studies [16], but similar pathology and an increase in proliferation has been shown in AVFs following venous angioplasty [17].

Paclitaxel exerts an antiproliferative effect by interfering with cell microtubule function [18]. Systemic administration of paclitaxel after angioplasty in the rat carotid artery showed that a significant reduction in neointimal proliferation could be achieved at doses much lower than antineoplastic levels [19]. In rat and human cultured cell models, paclitaxel inhibited vascular smooth muscle cell migration and proliferation [19, 20], consistent with its effects in vivo. As an alternative to systemic therapy, local drug delivery offers the advantages of allowing high local concentrations of drug at the treatment site while minimising systemic toxic effects. Proof of this possibility was initially shown using paclitaxel-coated stents in pig coronary arteries [21].

Recent advances in technology have allowed angioplasty balloons to be coated with paclitaxel. This allows local delivery of paclitaxel to the site of stenosis. A number of multi-centre randomised controlled trials in the coronary and peripheral arterial circulation have established the positive benefit of drug-coated balloons (DCBs) [22, 23]. A small pilot study has suggested efficacy in dialysis patients [24, 25]. In this study, 40 patients with dysfunctional AVFs or AVGs were randomised to receive either DCB or Plain Balloon Angioplasty (PBA). Primary unassisted patency (defined angiographically as a binary readout of <50% stenosis) in the DCB group was significantly better than the PBA group at 6 (70% v 25%) and 12 months (35% v 5%, $p<0.001$) respectively. This study may be criticised on a number of points. These include the use of an angiographic rather than a clinical endpoint, the lack of blinding and independent angiographic core lab analysis and the very small sample size originally intended to test non-inferiority only

(with a wide 15% non-inferiority limit). In addition, a range of balloons was used in the control group for post-dilation after the paclitaxel-coated balloons, and these were not universally high pressure and non-compliant. This may have added variability to the outcome. Furthermore, the inclusion of both AVFs (35%) and AVGs (65%) may have resulted in significant confounding, given the difference in survival rates associated to the two types of access. Despite these limitations, the results suggested that a further study of efficacy was warranted, which is what we propose here.

The PAVE trial is the first large scale randomised controlled trial designed to test superiority of DCBs in native haemodialysis access circuits. Further, the impact on patient quality of life will be performed.

1.2. Risks and benefits

The risks for patients taking part in this study are minimal. The plain balloon fistuloplasty is standard of care and the additional intervention will be the use of a paclitaxel-coated balloon or control balloon following this initial dilatation. The paclitaxel-coated balloons that will be used are CE marked and there have been no safety concerns with their use. In the specific context of haemodialysis AVFs, the pilot study performed did not raise any safety concerns [24].

1.3. Rationale for current study:

The overriding aim of this study is preservation of vascular access for haemodialysis with a reduction in restenosis and the need for repeat fistuloplasties.

Clinical Trial

Our hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic AVFs. As detailed in section 1.1, this hypothesis is supported by what is known of the effects of paclitaxel on the biology of neointimal formation, results in trials involving coronary and peripheral arteries, and a pilot study vascular access for haemodialysis.

This need for repeat procedures following angioplasty is expensive and inconvenient for patients and is needed in around 60% of patients during the first year [5]. As detailed in our sample size calculation we predict that the use of paclitaxel coated balloons will lead to an avoidance of the need for repeat angioplasty. Repeat angioplasties will also have a negative effect on patient quality of life and a reduction in these will be a benefit in addition to the reduction in cost.

Collection of patient samples

Patient blood samples will also be collected within the setting of the clinical trial. This will form an important resource for future laboratory based studies on biomarkers and AVF outcomes.

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2. Trial Objectives, Design and Statistics

2.1. Trial objectives

The purpose of this RCT is to compare the efficacy of additional paclitaxel-coated balloon fistuloplasty versus plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

Primary Endpoint:

Time to end of target lesion primary patency

This is defined as patency with no re-intervention to the area 5mm proximal to, within, and 5 mm distal to, the index treatment segment. Target lesion primary patency ends when *any* of the following occur: (a) clinically driven re-intervention to the treatment segment; (b) thrombotic occlusion that includes the treatment segment; (c) surgical intervention that excludes the treatment segment from the access circuit; (d) abandonment of the AVF due to an inability to retreat the treatment segment.

In order to confirm there is a significant stenosis prior to fistuloplasty, Duplex ultrasound is encouraged but is not mandatory.

After the study treatment, occasionally there may be recoil or rupture necessitating further balloon angioplasty or stent placement. Providing further angioplasty and/or stent placement achieves a residual stenosis of less than 30%, these patients will remain in the study.

Referral for a repeat procedure will originate from the clinical team who are unaware of whether the patient received treatment with a paclitaxel-coated balloon or uncoated control balloon.

A different radiologist to the one performing the index procedure will perform repeat procedures when possible but it is not possible to guarantee this. Therefore the radiologist performing the

repeat procedure may have knowledge of whether the patient was treated with drug-coated balloon or placebo.

In order to ensure that there is no bias in the final decision to proceed with the repeat intervention in patients who have not yet reached the primary endpoint, pre-procedure fistulograms prior to potential re-intervention will undergo independent analysis. This will allow confirmation that a significant stenosis was found in all patients who received a repeat intervention.

Secondary Endpoints:

1. Angiographically determined late lumen loss.

This is the difference between the diameter of the treatment segment post-procedure and the diameter at 6 months as measured by an independent core laboratory. If a patient has a repeat procedure to the treatment segment before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.

2. The rate of angiographic binary re-stenosis.

This is defined as the incidence of stenosis of at least 50% within the treated lesion at the 6 month follow-up fistulogram. If a patient has a repeat procedure to the index lesion before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.

3. Time to end of access circuit primary patency

The access circuit is defined as starting at the arterial anastomosis and ending at the cavoatrial junction. Access circuit primary patency ends when *any* of the following occur: (a) access circuit thrombosis, (b) an intervention (either radiological or surgical) anywhere in the access circuit, or (c) the access circuit is abandoned due to an inability to treat any lesion.

4. Time to end of access circuit cumulative patency

Access circuit cumulative patency ends when the AVF is abandoned, regardless of radiological or surgical intervention, with or without a thrombosis event. Multiple/repetitive treatments for stenoses that restore patency are compatible with cumulative patency.

5. Procedural success (residual stenosis ≤ 30% on completion fistulogram II, see section 4.4 below)

6. Number of thrombosis events

7. Total number of interventions

8. Adverse events (e.g. fistula rupture, infection)

9. Patient quality of life as assessed by the EuroQol EQ-5D generic health survey, and the disease specific Patient (or Palliative care) Outcome Scale symptom score-renal (POS-S Renal) [26].

2.2 Trial design

The study design used to achieve this will be a double-blind multicentre randomised controlled trial. We will recruit 211 patients over a three-year period. Patients will be followed up for a minimum of one year, and all patients will continue in the study until the last patient has

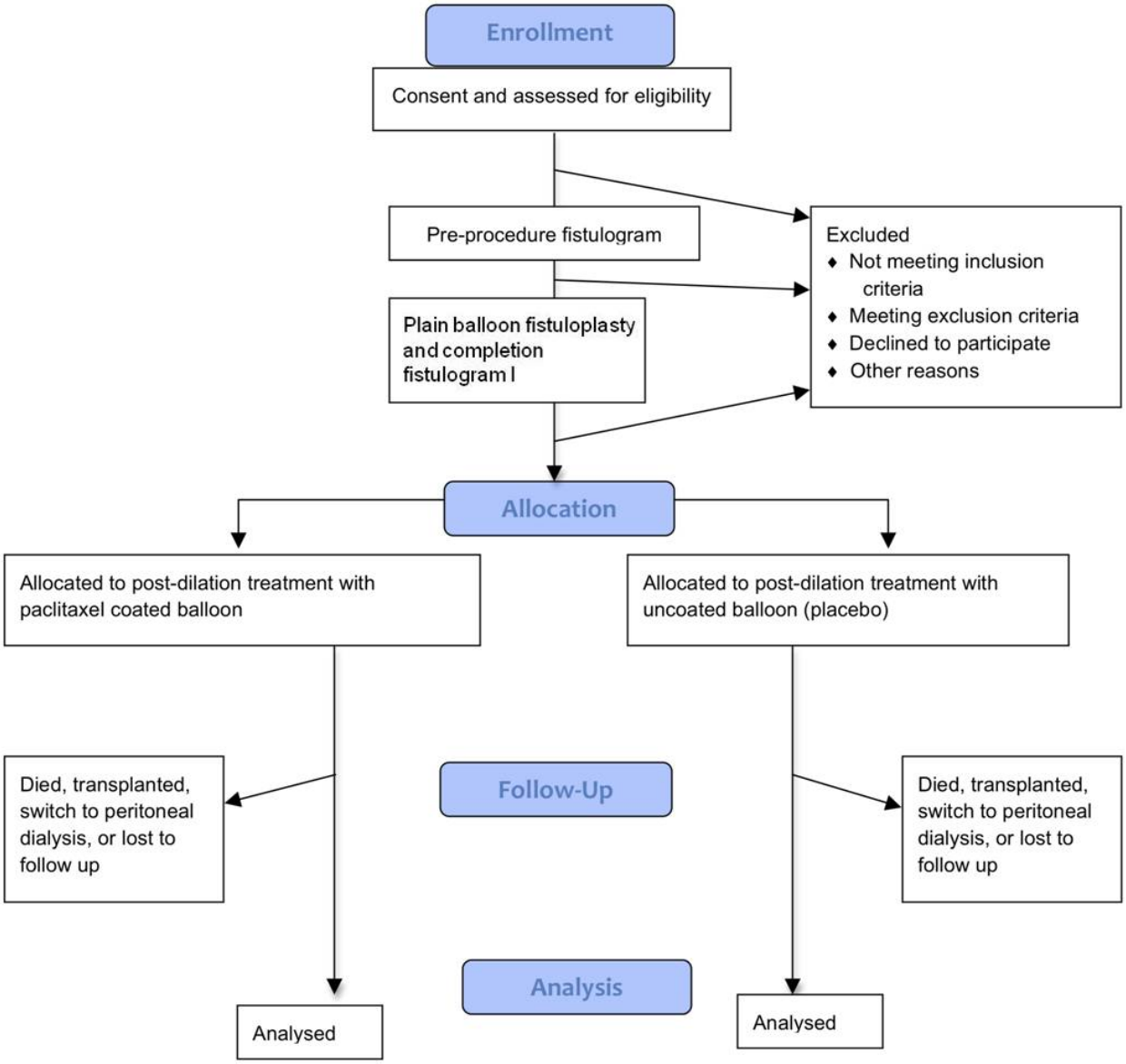
completed one year of follow up.

2.3 Trial schedule

	Pre-procedure	Procedure						Post-procedure ****														
								Day 1-3	mth 3	mth 6	mth 9	mth 12	mth 15	mth 18	mth 21	mth 24	mth 27	mth 30	mth 33	mth 36	mth 40	mth 44	mth 48
Patient registration and consent	x																						
Medical history (including indication for fistuloplasty)	x																						
Consideration of eligibility	x																						
Discussion and confirmation of potential eligibility with radiologist	x																						
Blood samples (taken on dialysis when possible)*****	x							x	x														
Pre-procedure fistulogram *		x																					
Plain balloon fistuloplasty			x																				
Completion fistulogram I *				x																			
Randomisation					X																		
Study treatment						x																	
Completion fistulogram II							x																
Protocol fistulogram										x													
Follow up assessments ** ***									x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments **** (POS-S Renal and EQ-5D)	x									x		x											

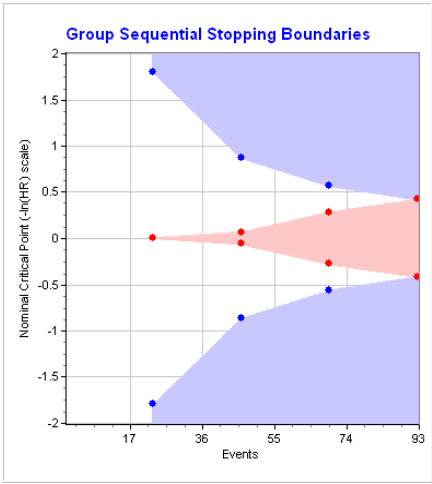
* Prior to randomisation, eligibility will be reviewed based on the radiological findings on both the pre-procedure fistulogram and completion fistulogram I
**At each follow up assessment information to be checked or collected will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, thrombosis events, patient medications, access circuit dysfunction, and adverse events
***Follow up will be for a minimum of 12 months and a maximum of 48 months
****Post-procedure study assessments occur every 3 months ± 1 month; Day 1-3 blood sample to be taken at next dialysis session after procedure, if this falls on a weekend then blood to be taken at the next dialysis session after this
****Failure to complete the Quality of life assessments will not be deemed a protocol violation
*****Bloods may also be collected pre and 1-3 days post the protocol fistulogram at Guy's and St Thomas' only

2.4 Trial flowchart



2.5 Trial statistics

Analysis of Primary Outcome: To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis. Primary analysis will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates. Patients with TLPP at the end of follow up will be considered censored, as will those who receive a renal transplant, switch to peritoneal dialysis or are lost to follow up before the study end. Kaplan-Meier plots, hazard-ratio and its confidence interval will be used to describe the results.



Analysis of Secondary Outcomes: Effects on secondary outcomes will be analysed using the same strategy for time-to-event variables, and generalized linear models for binary and continuous outcome measures, adjusting for the effects of relevant covariates when appropriate. Continuous variables will be checked for normality, transformed if necessary or otherwise analysed using a Wilcoxon-signed-rank test for independent samples.

Missing Values and Drop-outs: If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. Patients lost to follow up will be compared to patients who reach complete follow up in baseline characteristics and adverse events to test whether drop-outs are random.

Interim Analysis: Interim analysis of the primary outcome will be performed three times throughout the study, based on the cumulative number of failures of the treatment area, i.e. after 27, 54 and 81 events, expected approximately at 9, 14 and 19 months of study under the null, and at months 11, 17, and 23 under the alternative. Group sequential stopping boundaries have been calculated using a Lan-de-Mets spending function (with O'Brian-Fleming parameters), to allow early stopping for rejection of the null or the alternative hypotheses. Stopping in case of boundary crossing is non-binding.

3. Sample Size, Selection and Withdrawal of Subjects

3.1 Sample size

For the definition of the survival curve in the placebo balloon group, we assumed target lesion primary patency of 61%, 42%, and 35% at 6, 12 and 24 months respectively. This was consistent with published results [7] and with our own audit data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect size. Katsanos et al. [21] found a HR of 0.3 for TLPP at 6 months; however, the confidence interval was broad and the effect size is expected to be closer to the null when AVGs are excluded. Based on these assumptions, it is expected that the paclitaxel coated balloon group will show 78%, 65%, and 59% survival of TLPP at 6, 12 and 24 months respectively. Recruiting 211 patients, with variable follow up, a minimum follow up of 1 year, and three interim analyses, will provide 94% power to detect a statistically significant difference between the two groups in TLPP survival with 2-sided 5% type I error rate. It is expected that 108 patients will experience fistula failure during the follow up period.

The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, and recruitment of 2 patients per month (ppm) during the first three months, 8 ppm up to 7 months, and 12 ppm onwards. The expected accrual duration will be 36 months, and the maximum study duration (including follow-up) 50 months.

3.2 Inclusion criteria

1. Patients (18 years or over) who have a native AVF in the arm

2. An indication for a fistuloplasty as determined by the local clinical team

3. The access circuit is free of synthetic graft material or stents

4. A reduction of vessel diameter of ≥ 50% measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon

5. A residual stenosis ≤ 30% after plain balloon fistuloplasty

6. A treatment segment, containing one or more lesions, which can be treated with ≤120 mm of a single drug-coated balloon.

3.3 Exclusion criteria

1. Patient unable to give informed consent

2. Patient unwilling or unable to comply with all study-related procedures

3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure

4. One or more lesions outside the treatment segment, with a reduction of vessel diameter of ≥ 50% measured angiographically, in the same access circuit. The patient will also be excluded if any lesions outside the treatment segment are treated even if these are <50%

5. Location of stenosis central to the thoracic inlet

6. Thrombosed (failed) access circuit at time of treatment

7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children, within two years of study treatment

8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated

9. Known hypersensitivity or contraindication to paclitaxel

3.4 Criteria for withdrawal

Participants have the right to withdraw from the study at any time for any reason.

Participants will be withdrawn from the study if any of the following occur:

- Death of participant
- Participant receives a transplant
- Participant is changed from haemodialysis to peritoneal dialysis
- The fistula is ligated, abandoned, or thrombosed and not salvageable

The PI also has the right to withdraw patients from the study in the event of inter-current illness, AEs, SAE's, protocol violations, administrative reasons or other reasons, e.g. the participant is no longer being treated at a hospital included in the study.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Participants who wish to withdraw from 'treatment' will be asked to confirm whether they are still willing to provide study specific data and samples for scientific laboratory analysis according to the trial protocol.

4. Study Procedures

4.1 Screening procedures

Patients that may be eligible will be identified in a vascular access clinic and assessed by surgeons, specialist nurses and nephrologists.

In order to confirm there is a significant stenosis prior to angiography, a duplex ultrasound is encouraged but is not mandatory.

Consent will be taken after the patient has had sufficient time to read the information sheet, consider the trial and ask questions.

Eligibility criteria as listed above in section 3 will be assessed.

If the patient remains potentially eligible for the study, the radiologist who will perform the pre-procedure fistulogram will be informed.

4.2 The pre-procedure fistulogram

This will be take place immediately prior to the plain balloon fistuloplasty.

This will be performed in a dedicated Interventional Radiology suite equipped with digital subtraction angiogram, image overlay/roadmap post processing capabilities and ability to capture still and video

DICOM file data.

It will be performed through a sheath or cannula placed in the dialysis circuit according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second (fps) if possible. If the equipment will not allow 3 fps then 2 fps is acceptable.

2. The entire access circuit from anastomosis to central vein covered in up to 3 stages

3. Medial epicondyle of humerus visible bony landmark on lower arm acquisition, acromioclavicular joint on upper arm and central acquisitions

4. Measurement ruler in view

5. Lower arm acquisition to include:
   i. Anteroposterior Projection of anastomosis
   ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)

6. On the acquisition that best demonstrates the target lesion, the following measurements are made:
   i. Peripheral (close to anastomosis) reference vessel diameter
   ii. Minimum lumen diameter (MLD)
   iii. Central reference vessel diameter

The radiologist will assess all inclusion and exclusion criteria, to decide if the patient remains eligible for the study.

4.3 The plain balloon fistuloplasty procedure

This is performed as standard of care. Prior to treatment 3000-5000 IU of heparin is administered. For all patients treatment has two components. The fistuloplasty procedure is performed with a dedicated plain balloon (*Bard Dorado*). Only if the anatomy of the lesion precludes the use of the *Bard Dorado*, then an alternative high pressure balloon may be used, providing it has a rated burst pressure of >18 Atm. The following criteria will be met:

1. Sized to nominal vein diameter
2. Up to 24 Atm to ensure obliteration of the lesion waist
3. Minimum duration of balloon inflation 1 minute.

Completion fistulogram I is performed after the plain balloon fistuloplasty to ensure adequate therapy according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second (fps) if possible. If the equipment will not allow 3 fps then 2 fps is acceptable.

2. Acquisition that demonstrates the target lesion matched as close as possible to the respective pre-procedure fistulogram acquisition
3. Measurement ruler in view

4. A core laboratory will make the following measurements at a later stage (these are not made by the radiologist performing the procedure)
    i. Peripheral (close to anastomosis) reference vessel diameter
    ii. Minimum lumen diameter (MLD)
    iii. Central reference vessel diameter

The radiologist will assess all inclusion and exclusion criteria to decide if the patient remains eligible for the study.

4.4 Randomisation procedures

Randomisation will be at the level of the individual participants, minimising on radiologist performing the study procedure, whether the participant is currently on haemodialysis or not, and whether the participant has had a previous radiological intervention in the access circuit or not. This is performed with an 80% probability of allocating to the arm which reduces the imbalance. The allocation sequence will be generated dynamically. This way, the next allocation will only be generated and become known upon actioning a request from the study site staff.

Minimisation will be implemented using an independent web-based randomisation system hosted at the UKCRC registered clinical trials unit at KCL. Site staff will access the service via www.ctu.co.uk using a computer in the angiography room or an office nearby. It will be performed by the radiologist or their nominee, who will log into the system, enter the participant ID number, initials, date of birth, recruiting radiologist, whether the participant is currently on haemodialysis or not, and whether the participant has had a previous radiological intervention in the access circuit or not. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention. Each randomiser will have unique user access, provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed.
Once randomised, the system will automatically generate a confirmation email, which will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study.

If it is not possible to use the randomisation system, randomisation may occur using the toss of a coin in order to avoid losing the patient from the study. *This should only be needed, if at all, in specific and rare situations such as the CTU server being inaccessible.* This will be performed by two people with heads denoting drug-coated balloon, and tails denoting placebo. The CTU must be informed of the coin randomisation as soon as possible.

4.5 Study treatment

In the intervention arm, the second component is insertion of a single drug-coated balloon (*Bard Lutonix*).

If a single plain balloon was inflated at one location, the drug-coated balloon must be of identical diameter to the plain balloon and a minimum of 1 cm longer than the plain balloon (5 mm at either end).

In some cases more than one plain balloon may be used, or the same balloon may be inflated at different locations (eg to treat tandem lesions). In these cases, the drug-coated balloon must be of identical diameter to the largest diameter plain balloon used. The length of the drug-coated balloon must be a minimum of 1cm longer (5mm either end) than the entire segment of vein that has been in contact with plain balloon.

The drug-coated balloon will be inflated to nominal pressure at the lesion location for a minimum of 1 minute duration.

Instructions for use of the drug coated balloon are stringently adhered to ensure appropriate preparation and handling of the device.

In the control arm, an identical procedure is followed, but using a single placebo balloon that is not drug coated (*Bard Ultraverse)*.

In both arms, image overlay/roadmap will be utilized to ensure that there is no geographical mismatch between the segments treated with the high and low-pressure balloons.

A completion fistulogram is performed (completion fistulogram II) to confirm no angiographically visible effect after treatment with the drug-coated or placebo balloon, according to the same specifications as fistulogram I in section 4.3. Procedural success is defined as a residual stenosis ≤ 30% on completion fistulogram II.

The data file(s) containing the initial pre-procedure fistulogram, and completion fistulogram I and II will be sent to the lead study site with the patient's name replaced by the trial ID, and with each of the above groups of images clearly identified. Completion fistulogram II will then be sent to the independent angiographic laboratory for analysis.

4.6 Study assessments

These will occur every 3 months ± 1 month. Follow up will be variable but for a minimum of 1 year and will continue for each patient while the study remains open. It is expected that the study will remain open for 4 years. These will involve a clinical assessment to take place either face-to-face or via a telephone conversation. Any face-to-face meetings will usually coincide with dialysis to avoid additional patient travel.

Data recorded for each study assessment will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, patient medications, and adverse events.

At the 6-month study assessment, the trial team will check if referral for re-intervention is being considered based on clinical concerns.

The decision to perform a protocol fistulogram or not to, will be confirmed with the PI after discussion with relevant clinical colleagues, and a consideration of the points discussed in 4.7.1.

4.7 Radiology Assessments

4.7.1 The 6 month protocol fistulogram

Patients may be reimbursed for travel costs.

The protocol fistulogram will take place within 6 weeks of the 6 month study assessment if no clinical concerns are identified.

If clinical concerns are identified, then the protocol fistulogram may be delayed while the fistula is

assessed. If the outcome of this assessment is that an angiogram or re-intervention is not indicated, the patient may then have a protocol fistulogram scheduled. This must be no later than 9 months after the study intervention and treatment.

If the outcome of this assessment is that an angiogram or re-intervention is indicated, then a fistulogram ±plasty will be performed according to usual clinical practice and the patient will not undergo a protocol fistulogram.

If a patient has required a repeat fistuloplasty to the treatment segment at or before 6 months then they will not undergo the 6 month protocol fistulogram.

If a patient declines the 6 month protocol fistulogram or does not have it for another reason, this will not be considered a protocol violation and the patient may continue in the study.

The 6 month protocol fistulogram *must* be performed by a radiologist other than the one who performed the index procedure to ensure that they are blind to which trial arm the participant belongs. With forward planning this should be possible but if it is not then the protocol fistulogram should not be performed.

The 6 month protocol fistulogram will be a diagnostic study only unless an unsuspected stenosis is found and the radiologist believes that it would be unethical not to intervene. This will not be considered a protocol violation and a fistula intervention form will need to be completed. The 6 month protocol fistulogram will follow the same specifications as the pre-procedure fistulogram in section 4.2.

The 6 month protocol fistulogram will be considered to be exclusively trial data. The result of the 6 month protocol fistulogram will not be made available (verbally or in writing) to the clinical team responsible for considering future referral of the patient for an intervention. The images will also not be available on the local radiology system. The images will be sent to the lead site in order to be forwarded to the independent core laboratory with the patient's name replaced by the trial ID.

4.7.2 Fistulograms performed for a clinical indication

In patients who have not yet reached the primary endpoint of the trial, pre-procedure fistulograms will follow the same specifications as the pre-procedure fistulogram specifications in section 4.2. The image file will be sent to the lead site with the patient details replaced by the trial PIN. This will be sent regardless of whether or not the fistulogram is followed by a fistuloplasty.

In patients who undergo an intervention, before 6 months, to the treatment segment, the pre-procedure fistulogram will be used (by the independent core laboratory) in place of the 6 month protocol fistulogram for analysis of the angiographic secondary endpoints.

4.8 End of Study Definition

The clinical trial will end when 211 patients have been recruited and all patients have completed at least one year of follow up.

The trial may be prematurely discontinued by the Sponsor, Funder, Chief Investigator or TSC on the basis of new safety information or for other reasons given by the DMC, TSC, REC. The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected.

5. Laboratories

5.1 Laboratory tests

There are no local laboratory tests that are required to provide data that directly relate to trial endpoints. A 10 ml blood sample will be requested at the three timepoints stated in the trial schedule (2.3), and is to be sent to the local clinical laboratory for a full blood count and to check the C-reactive protein level. If patients decline some or all of these samples, it will not be considered a protocol violation.

Blood (up to 90 ml) may be taken at each of the time points in the Trial Schedule in 2.3. These will be sent to the research laboratory of the CI where the blood will be separated. Research blood samples should not be taken from patients who are known to be hepatitis B sAg, hepatitis C IgG/ RNA, or HIV positive. DNA and RNA will be stored. Cells will be stored in aliquots in liquid nitrogen until thawed for analysis. Serum and/or plasma samples will be stored at -20'C or -80'C until thawed for analysis. Transport, separation and storage will be according to Standard Operating Procedures. It will not be a considered a protocol violation if any of the blood samples are not taken, or are taken at different time points to those specified and patients may continue on the study.

If a patient is enrolled but not randomised, the patient will not continue in the clinical trial. However blood samples may continue to be taken for laboratory research (at the same time points as for patients remaining in the trial). Clinical data may also be recorded though this may not be on the eCRF system.

5.2 Independent Core Lab Analysis

The completion fistulogram II (taken after treatment with the DCB or placebo low pressure balloon) will be compared with the protocol 6 month fistulogram or with the pre-procedure fistulogram taken prior to a clinically driven re-intervention at the treatment segment if this is before 6 months. These will be analysed by an Independent Core Lab for the angiographic secondary endpoints.

In addition, in patients who have not yet reached the primary endpoint of the trial, clinically-driven pre-procedure fistulograms will be sent to the Independent Core Lab for analysis if they were performed by a radiologist who is not blind to the study treatment. This will be sent regardless of whether the fistulogram is followed by a fistuloplasty.

6. Assessment of Safety

We have been informed by the MHRA that the PAVE protocol does not fall within the Clinical Trial Regulations and therefore is not a drug trial. In addition, the drug-coated balloon is a CE-marked medical device, so prior regulatory approval from the MHRA is not needed.

Safety reporting will be in keeping with the requirements for research other than Clinical Trials of Investigational Medicinal Products.

A Serious Adverse Event (SAE) is an untoward occurrence that:

a) results in death
b) is life-threatening
c) requires non-elective hospitalisation or prolongation of existing hospitalisation
d) results in persistent or significant disability or incapacity
e) consists of a congenital anomaly or birth defect

f) is otherwise considered medically significant by the investigator.

All SAEs will be reported by the local investigators on the SAE form to the Chief Investigator, immediately they become aware and within 24 hours at most. A planned or non-elective hospital admission does not need to be reported as an SAE unless the PI decides it should be.

Although it is not an SAE, any pregnancy or fathering of children that occurs within 2 years of the study treatment will be reported via the SAE system as below.

Reports of SAEs will be reviewed by the CI within 24 hours to assess whether the event is related to the research procedure and unexpected (a SUSAR) and if so, it will be onward reported to the REC and DMC within 15 days, in the format prescribed by NRES and published on the website.

Since the study treatment is local and not systemic, non-serious adverse events will be defined as events that the PI considers are directly related to the vascular access that has been treated. These should be recorded throughout the trial and will be captured in the eCRF at each study assessment.

7. Data Monitoring Committee

The membership will be decided by the CI and approved by the NIHR. The DMC includes a statistician and two other independent experts. They will receive a report of recruitment, serious and non-serious adverse events and a summary of accumulated clinical data from the trial statistician, and will meet in person or by telephone. They will report to the TSC who will usually meet in the two weeks following the DMC meeting. The DMC will meet at least annually during the study, approximately 2 weeks prior to the TSC. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The DMC is advisory to the TSC. The DMC charter will be drafted and agreed prior to recruitment. The Trial Statistician will prepare reports to the DMC.

8. Trial Steering Committee

The TSC will be convened in the post-award period. The membership will be decided by the CI and approved by the NIHR. The chair will be an independent expert. Members will include the CI, a patient representative, and two other independent experts. The TSC will meet at least annually during the study, approximately 2 weeks after the DMC. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The TSC is an executive committee. Terms of reference of the TSC will be agreed and documented prior to start of recruitment. The Trial Manager will prepare reports to the TSC.

9. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework.

This protocol and related documents will be submitted for review to the London-Chelsea Research Ethics Committee (REC).

The Chief Investigator will submit a final report at conclusion of the trial to the sponsor and the REC.

Annual progress reports will be submitted to the main REC for the study.

10. Data Handling

All samples will be anonymised before laboratory analysis. No patient-related data will be held in research laboratories.

During the study, any paper documents will be held in a locked filing cabinet in a locked office and retained for a minimum of 5 years following the end of the study.

Clinical and research data for the study will be stored on the eCRF system, hosted at the King's Clinical Trials Unit, KCL. The eCRF (InferMed MACRO) is GCP and FDA 21 CFR Part 11 compliant. Data entry staff at site will be provided with unique usernames and passwords to the system and will be trained in data entry by the trial manager. The trial manager will visit sites to review data on the system, raise discrepancies and confirm source data verification checks. All requests for access to the data entry system must be authorised by the trial manager. All requests for data exports must be authorised by the trial statistician. The trial manager will work with the CI and the trial statistician to ensure data is checked and cleaned on an ongoing basis and will confirm all data checks have been completed before database lock.

The investigators and the institutions will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other relevant documents (i.e. patients' case sheets, blood test reports, X-ray reports). Record keeping will be the responsibility of the investigators.

11. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The chief investigator will review all presentations and publications arising from this study and decide authorship in accordance with accepted guidelines.

12. Insurance / Indemnity

The study will be indemnified by King's College London for negligent and non-negligent harm. In addition, the recruiting sites will have NHS indemnity.

13. Financial Aspects

The NIHR have supported the study through an EME programme grant award. The fistuloplasty balloons are supplied by C.R. Bard, Inc. who have no other role in the design, running, or analysis of the trial.

PAVE

VERSION CONTROL DOCUMENT – keep at front of Trial Master File

THE MOST UP-TO-DATE VERSION OF EACH DOCUMENT MUST BE PLACED UPPERMOST IN THE FILE – Retain all earlier versions for audit purposes and mark: 'Superseded by Version (No) on (date)' to avoid accidental use of wrong version.

Study Title (full):	Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access		
Study Title (short):	PAVE		
Study Rec ref:	15/LO/0638	**Chief Investigator:**	Dr Michael Robson

PROTOCOL

VERSION No.	DATE	DATE APPROVED BY ETHICS	Changes
2.0	21 / 07 / 2015	18 / 08 / 2015	Version 2 it was approved and live before the first site opened to recruitment.
3.0	20 / 10 / 2015	03 / 11 / 2015	Wording in the protocol describing trial procedures have been changed for clarification: • "high pressure" changed to "plain" when describing the balloon used in the initial procedure • "treatment area" changed to "treatment segment" • The stratifier "whether or not the participant has had a previous intervention to the treatment segment" has been changed to "whether or not the participant has had a previous intervention in the access circuit" • The definition of the primary endpoint has been changed from "this is defined as patency with no reintervention to the area 5mm proximal within, and 5 mm distal to, the index treatment segment" to "this is defined as patency with no reintervention to the area 5mm proximal to, within, and 5 mm distal to the index treatment segment" It has been clarified in inclusion criteria 1 that eligible participants should have an AVF that has been in use for 12 "consecutive" dialysis sessions (also listed in IRAS QA171) An additional secondary endpoint, "total number of interventions" has been added (also listed in IRAS QA11). The treatment procedure has been further clarified to ensure uniformity over all sites: • The length of the treatment or placebo balloon relative to the plain balloon has been stated to ensure appropriate application of the treatment

			• The dimensions of the treatment or placebo balloon should be determined by the largest plain balloon used in the procedure prior to the study treatment • A further fistuloplasty immediately after study treatment to treat recoil does not constitute meeting the primary endpoint The time in which the day 13 blood sample can be taken has been further defined in order to be more flexible, to account for out of office hours dialysis sessions The randomisation method has been specified as the minimisation method. We are using this method for three reasons: • Minimisation allows other radiologists at a site who don't perform the index procedure, and who will evaluate primary outcome, to be kept blinded. Using the alternative method, stratified block, where stratification would be i) by study site, and ii) whether or not the participant has had a previous intervention to the access circuit, the randomisation system would send all radiologists at a site the unblinded result. This is a limitation of the randomisation system we are using, but building a bespoke system would greatly delay the trial, thus using minimisation is appropriate. • Minimisation ensures balance between groups, avoiding confounding due to radiologists effect. • Minimisation is preferable to stratified block due to the large number of strata that result from the two stratifiers, and especially as the number of radiologists involved in the trial could change.
4.0	23 / 11 / 2015	N/A	Non-substantial amendment to the protocol including the following changes: - a change in trial statistician - re-wording in order to clarify procedures but no major change to warrant a substantial amendment.
5.0	08/03/2016	08/04/2016	Protocol changes: Eligibility Criteria (study synopsis and section 3.2; IRAS QA17-1) • Inclusion criterion 1 has been changed to include all patients who have a native AVF in the arm, regardless of whether they are on haemodialysis or not. Previously we only included those patients who have been on haemodialysis for 12 consecutive sessions. These patients represent a prevalent population that would be relevant to the study. Most participants will start dialysis during the follow-up period and so the clinical endpoints of the trial will be unaffected. Even in those participants who do not start dialysis, their fistula can be assessed clinically and therefore clinical endpoints can still be assessed. Whether the participant is on haemodialysis or not at the time of randomisation will be an additional minimisation factor (section 4.4). • The Participant Information Sheet, section 'Why have I been invited to take part?' has been

			amended to reflect this change. The PIS version referenced on the consent form has been updated as a result. Plain Balloon Fistuloplasty Procedure (section 4.3): • We have specified that an alternative high pressure balloon to the one specified can be used only if the anatomy of the lesion is such that doesn't allow the specified balloon to be used initially. We have changed this so that participants with this type of lesion are not excluded in error. Subsequent changes in section 4.5 Study Treatment relate to this specification. • For clarification, we have specified that a total of 3 plain balloon fistuloplasty treatments are allowed prior to the study treatment. Fistulograms performed for a clinical indication (section 4.7.2) • We have clarified this section to ensure that all sites clearly understand which fistulograms images are required.
6.0	07/07/2016	31/08/2016	1. Change in Project Manager (pg 2). Mrs Vikki Semik has resigned from her post and has been replaced by Dr Leanne Gardner as the Project Manager for PAVE. 2. Change in inclusion and exclusion criteria to increase participant eligibility rates. An audit of eligibility rates for PAVE indicated that a considerable proportion of patients were ineligible for the trial due to synchronous lesions in their access circuit. As there are longer drug-coated balloons (greater than 60mm) available for use in the trial, we would like to include participants with one or more lesions than can be treated with up to 120mm of a single drug-coated balloon. This will improve eligibility rates and increase recruitment to the trial without the requirement for changes analysis of trial outcomes. Inclusion criteria 6 has been altered to include participants with a treatment segment containing one or more lesions that can be treated with greater than or equal to 120mm of a single drug-coated balloon (pg 4 and 15). Exclusion criteria 4 has been altered to exclude patients with one or more lesions outside the treatment segment (pg 4 and 15). 3. Removal of details from the plain fistuloplasty procedure to increase participant eligibility rates. After consultation with a number of interventional radiologists, it was decided that if further balloon fistuloplasty treatment is required to obtain a positive result (residual stenosis is ≤ 30%), that the administration should not be restricted to two more times. Thus this paragraph was removed from the protocol (pg 17). 4. Clarification of who will be performing the measurements required for the analysis of fistulograms performed in the trial. Details indicating that it will be a core laboratory that will make the fistulogram measurements have been added to the protocol (pg 18). This was added to the protocol because the interventional radiologists were unsure as to whether or not they were required to take these measurements. 5. Details regarding the input of required information into the randomisation system have been added to the randomisation procedure section. In a previous amendment, we added that participants who were not currently on haemodialysis

			were eligible for the trial. Further detail was required in the protocol to indicate to the radiologists that this data must be entered into the randomisation system prior to randomising the participant (pg 18). 6. Clarification of the length of time participants will be on the study: Additional information has been added to the protocol to indicate that participants will remain in the study until the last patient recruited has undergone one-year of follow up. The expected duration of the trial is 3 years but it will remain open until recruitment is complete and the last recruited patient has undergone one year of follow up. 7. Clarification of procedures relating to the 6-month protocol fistulogram. We have altered the protocol to indicate that the decision to perform a protocol fistulogram, or not must be confirmed with the PI after discussion with relevant clinical colleagues (pg 19). We have also indicated that the 6-month protocol fistulogram must be performed within 6 weeks of the 6 month study assessment. This was increased from 2 to 6 weeks because additional time is required is some cases for the confirmation that a protocol fistulogram can be performed or not (pg 19). We have indicated that participants may be reimbursed for their travel expenses for attending the hospital for their 6-month protocol fistulogram. These participants will be attending the hospital specifically for this research-related procedure and not for clinical reasons. Thus we believe reimbursement for their travel expenses is justified in this case (pg 19). 8. Clarification of procedures relating to fistulograms performed for a clinical reason. In section 2.1 (page 10) we have clarified that an independent assessment of the fistulogram will be performed though this may not necessarily be a core laboratory analysis in all cases. In section 4.7.2 (p20) we have clarified that all images from fistulograms performed for a clinical indication will be sent to the lead site. Some of these (prior to 6 months) may be used for to assess angiographic secondary endpoints as stated. Some may be sent to the independent core laboratory to demonstrate a lack of bias (as stated in section 5.2). Others may be used for quality control by the lead site. 9. Collection of blood samples and clinical data from patients who have consented to the trial but are not randomised. We have added to the protocol that blood samples may continue to the taken and clinical data recorded, from consenting patients for laboratory research. These samples will be used for mechanistic studies that are planned on samples from patients who remain in the PAVE trial. Samples from patients excluded from the trial will remain useful for these studies which will examine factors in the blood pre and post fistuloplasty. The patient information sheet has also been amended to clarify this. 10. Further clarification that the intervention procedure must be performed with only a single non-drug-coated or drug coated balloon. We have added the word "single" in two sentences of the Study Treatment section (pg. 18) to ensure that the radiologists are aware that they are only to use a single non-drug-coated or drug-coated balloon for the intervention. 11. Changes to study documentation including PIS and consent form have also been made.
7.0	26/01/2017	21/03/2017	Study Synopsis: Exclusion criterion Point 4. (page 4)

			Additional detail has been added to criterion 4 to exclude patients if they have any additional lesions outside the treatment segment that are treated even if the reduction of vessel diameter of these lesions are <50%. 3.3 Exclusion Criteria Point 4. (page 4) Additional detail has been added to criterion 4 to exclude patients if they have any additional lesions outside the treatment segment that are treated even if the reduction of vessel diameter of these lesions are <50%. 3.4 Criteria for withdrawal (page 16) This section has been amended to update the criteria for withdrawal from the study. Participants will now be withdrawn from the study if their fistula is ligated, abandoned, or thrombosed and not salvageable. We no longer need to follow up these patients because the fistula that contained the treated lesion is no longer functioning and therefore does not need to be assessed. 4.1 Screening procedures (page 16) In a previous amendment (Amendment 4 08/03/2016) we were given approval to consent participants in less than 24 hours prior to the procedure providing that the patients had sufficient time to considered taking part in the trial. This would allow us to take consent on the same day as the initial procedure, which is sometime necessary. These changes were approved by the REC. However this information was not updated in the protocol. These changes have now been made to the protocol indicating that consent will be taken after the patient has had sufficient time to read the information sheet, consider the trial and ask question. 4.1 Screening procedures (page 16) All fistulograms are to be performed as digital subtraction acquisitions at 3 frames per second (fps). However at some units this is not possible. Thus we have indicated in the protocol that if equipment will not allow 3 fps then 2 fps is acceptable. The inclusion and exclusion criteria are examined at a number of different times during the screening period. Thus we have removed details when each of the criterion should be examined because most criterion are examined on a number of occasions. 4.2 The pre-procedure fistulogram (page 17) Following the pre-procedure fistulogram the radiologist will assess all inclusion and exclusion criteria to decide if the patient remains eligible for the study. This has been clarified as some criterion need to be re-assessed following the procedure. 4.3 The plain balloon fistuloplasty procedure (page 18) Following the plain balloon fistuloplasty procedure, the radiologist will again assess all inclusion and exclusion criteria to decide if the patient remains eligible for the study. This has been clarified as some criterion need to be re-assessed following this particular procedure. 4.6 Study assessments (page 19) For clarification purposes regarding the 6 month study assessment, details about the requirements for the 6-month protocol fistulogram have been removed from this section and added to the following section 4.7.1. 4.7.1 The 6 month protocol fistulogram (page 20)

			This section has been rewritten for clarity. It indicates that the protocol fistulogram is performed if there are no clinical concerns identified and that it can be delayed while the fistula is assessed. Following assessment and if there are no concerns the 6-month protocol fistulogram can be performed no later than 9 months after the study intervention took place. If there are clinical concerns following assessment, then the 6 month protocol fistulogram will not take place and normal clinical practice will proceed. Patients may be reimbursed for travel costs if they have their 6 month protocol fistulogram (this was previously approved by the REC). 5.1 Laboratory test (page 21) Previously, the REC had approved a reduction in the number of times a 10ml blood sample will be taken from four timepoints to three timepoints. This was updated in Table 2.3 but was not changed in the text of this section. This has now been updated. Blood samples are being taken before and after the study procedure and at the 3-month timepoint.
8.0	13/12/2017	28/02/2018	Section 2.1 Primary Endpoint: Additional information has been added to the protocol for defining the primary endpoint. This information more clearly defines the assumptions required for time to end of target lesion primary patency. Section 4.5 Study Treatment: Additional information regarding the treatment procedure and use of plain balloons and treatment balloons has been added to the protocol. This was required to more clearly describe how the procedure is carried out correctly and to limit the number of protocol deviations due to inadequate description of the procedure. The additional text is highlighted in version 8 of the protocol attached.
9.0	12/09/2018	21/12/2018	Changes to the Protocol: Contact List: (Page 1): Updated details of the Sponsor and Co-Sponsor have been added to this section. The following changes have been made to the protocol to incorporate the additional 11 month study period, and to provide clarity of information: Section 2.2 (page 11) Previous Text: We will recruit 211 patients over a two-year period. New text: We will recruit 211 patients over a three-year period. Section 2.3 Trial Schedule (page 12) Following approval of the study extension, we have increased the number of follow up assessments in the Trial Schedule to month 48. We have also updated the Trial Schedule to confirm that failure to complete the Quality of life assessments will not be deemed a protocol violation. We have also added to the Trial Schedule that blood samples may also be collected pre and 1-3 days post the protocol fistulogram at Guy's and St. Thomas' only. Section 3.1 (page 14) Previous Text: The expected accrual duration will be 22 months, and the maximum study duration

			(including followup) 34 months. New text: The expected accrual duration will be 36 months, and the maximum study duration (including follow-up) 50 months. Section 4.6 (page 19) Previous Text: It is expected that the study will remain open for 3 years. New text: It is expected that the study will remain open for 4 years. Section 5.1 (page 21) For clarity, the second paragraph of this section has been updated to say Trial Schedule rather than table of events. Previous Text: Blood (up to 90 ml) may be taken at each of the time points in the table of events in 2.3. New text: Blood (up to 90 ml) may be taken at each of the time points in the Trial Schedule in 2.3.

PAVE Statistical Analysis Plan

Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access (PAVE)

A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel-assisted balloon angioplasty of venous stenosis in haemodialysis access

Statistical Analysis Plan

Version 1.0

Version 1.0 started: 01/03/2016

ISRCTN: 14284759

This SAP has been written based on Protocol V4.0

Trial Statistician: Emily Robinson

Signature..... Date 19/04/2016

Chief Investigator: Dr Michael Robson

Signature..... Date 12.4.16

Trial Steering Committee Chair: Dr Richard Haynes

Signature..... Date 8/3/16

Data Monitoring Committee Statistician: Dr Isabel Reading

Signature..... Date 05/04/2016

PAVE Statistical Analysis Plan

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PAVE Statistical Analysis Plan

1 QUANTITATIVE ANALYSIS PLAN

This document details the presentation and analysis strategy for the primary paper reporting results from the PAVE trial. Subsequent papers of a more exploratory nature will not be bound by this analysis plan but will be expected to follow the broad principles laid down for the principle paper(s). The principles are not intended to curtail exploratory analysis or to prohibit sensible statistical and reporting practices. Rather, they are intended to establish the primary scientific objective of the study, including the primary comparison and primary outcome and the strategy that will be followed as closely as possible, when analysing and reporting the trial.

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1.1 Description of the trial

This is a double-blind, multicentre RCT to assess the efficacy of additional paclitaxel-coated balloon angioplasty compared to high-pressure balloon angioplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

1.1.1 Principal research objectives to be addressed

The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.

Primary objective
To assess time to end of target lesion primary patency (TLPP) following study treatment angioplasty.

Secondary objectives
To assess the difference between the two groups in:

1. Angiographically determined late lumen loss

2. The rate of binary angiographic re-stenosis
3. Time to end of access circuit primary patency
4. Time to end of access circuit cumulative patency
5. Procedural success
6. Number of thrombosis events
7. Number of fistula interventions
8. Adverse events
9. Patient quality of life assessed by EQ-5D and POS-S Renal

A detailed description of trial objectives can be found in protocol section 2.1.

1.1.2 Trial design including blinding

The study is a double-blind multicentre randomised controlled trial, aiming to recruit 211 patients over a two-year period. Randomisation will be at the level of the individual participants, minimising on radiologist performing the study procedure and whether the participant has had a previous radiological intervention in the access circuit or not. Follow up will be variable and for a minimum of one year; and all patients will continue in the study until the last patient has completed one year of follow up.

1.1.3 Method of allocation of groups

Recruitment and pre-screening procedures are described in the protocol sections 4.1-4.3. Once the patient has completed the pre-procedure fistulogram, high-pressure balloon fistuloplasty, and the completion fistulogram I, the radiologist will assess if the residual stenosis is ≤30%; if this is the case then the patient will proceed to randomisation.

Randomisation will take place via a web based randomisation service, hosted at the UKCRC registered clinical trials unit at KCL. Site staff will access the service via www.ctu.co.uk using a computer in the angiography room or an office nearby. It will be performed by the radiologist performing the study procedure, or their nominee, and each randomiser will have unique user access. Access will be provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed and relevant documentation regarding the individuals has been collected. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention.

As explained in 1.1.2, patients will be randomized using minimisation; this is performed with an 80% probability of allocating to the arm which reduces the imbalance. The allocation sequence will be generated dynamically so that the next allocation will only be generated and become known upon actioning a request from the study site staff. Once randomised, the system will automatically generate an email confirmation, which will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study: an unblind email is received by the trial manager and the radiologist who is performing the randomisation; and a blind email is received by the principal investigator and research nurses.

If it is not possible to use the randomisation system randomisation may occur using the toss of a coin in order to avoid losing the patient from the study. This should only be needed, if at all, in specific and rare situations such as the CTU server being inaccessible. This will be performed by two people with heads denoting drug-coated balloon, and tails denoting placebo. The CTU must be informed of the coin randomisation as soon as possible.

1.1.4 Duration of the treatment period

Study treatment is described in detail in the protocol section 4.5. This is a one-off treatment that is administered within one study visit. Any repeat intervention is considered an event and therefore the end of the follow up.

1.1.5 Frequency and duration of follow-up

Study assessments will take place every 3 months. Follow up will be variable but for a minimum of 1 year and a maximum of 3 years. These will involve a clinical assessment to take place either face-to-face or via a telephone conversation. Any face-to-face meetings will usually coincide with dialysis to avoid additional patient travel.

1.1.6 Visit windows

At the time of each 3-month study assessment, an allowance of one month will be given either side to measure follow-up. This one month visit window will be the same for recording data throughout the follow-up period, i.e. 3-36 months post randomisation.

1.1.7 Eligibility screening

Patients that may be eligible will be identified in a vascular access clinic and assessed by surgeons, specialist nurses and nephrologists. In order to confirm there is a significant stenosis prior to angiography, a duplex ultrasound is encouraged but is not mandatory. At least 24 hours after being given the patient information sheet and before entering the angiography room for the pre-procedure fistulogram, consent will be taken and eligibility criteria will be assessed.

Inclusion and exclusion criteria are described in sections 3.2 and 3.3 of the protocol.

The radiologist who will perform the pre-procedure fistulogram, high-pressure balloon fistuloplasty and completion fistulogram will be informed that the patient is potentially eligible for the study, and they will assess the remaining eligibility criteria.

1.1.8 Measures

Baseline
The following demographics will be measured at baseline:

- Age (years)
- Gender (male; female)
- Ethnicity (White; Black; Asian; Mixed; Other)

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The following clinical details will be measured at medical history screening:

- Current diabetes diagnosis (yes; no)
- Patient smoking history (current smoker; former smoker; never smoked)
- Coronary artery disease (yes; no)
- Peripheral vascular disease (yes; no)
- Time since end-stage kidney failure (months)
- Previous renal transplant(s) (number)
- Total accumulated time with a functional renal transplant (months)
- Total accumulated time patient has spent on haemodialysisis (months)
- Total accumulated time patient has spent on peritoneal dialysis (months)
- Location of fistula (right arm; left arm)
- Type of native fistula (Radio-cephalic; Brachio-cephalic; Basilic vein transposition; Ulnar-cephalic)
- Time since fistula was formed (months)
- Time since fistula was first used (months)
- Current access circuit previously had a thrombosis (yes; no)
- Previous surgical interventions to the current access circuit (number)
- Previous fistuloplasties to the current access circuit (number)
- Primary indication for the index procedure (inadequate dialysis; poor fistula blood flow; prolonged bleeding; high venous pressures; low arterial pressure; difficulty needling; other evidence of fistula dysfunction)

The following clinical details will be measured at the pre-procedure fistulogram:

- Location of stenosis (juxta-anastamotic; venous segment; cephalic arch; after cephalic arch and not beyond the thoracic inlet; beyond the thoracic inlet)
- Degree of stenosis (5%)
- Length of stenosis (mm)
- Radiologist (initials)

The following clinical details will be measured at the treatment fistuloplasty:

- Index lesion vessel diameter (mm)
- Diameter of plain balloon used (mm)
- Length of plain balloon used (mm)
- Pressure to which used plain balloon was inflated (atm)
- Number of unsuccessful attempts at plain balloon fistuloplasty (0-2)
- Complications due to plain balloon fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Diameter of study treatment balloon used (mm)
- Length of study treatment balloon used (mm)
- Pressure to which study treatment balloon was inflated (atm)
- Complications of the study treatment fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Residual stenosis still 30% or less after study treatment (yes; no)
- Further fistuloplasty performed after study treatment (yes; no)

- Type of balloon from further fistuloplasty (Dorado; other)
- Diameter of balloon from further fistuloplasty (mm)
- Length of balloon from further fistuloplasty (mm)
- Residual stenosis 30% or less after further fistuloplasty (yes; no)
- Complications due to further fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Radiologist (initials)

Primary outcome measures
The primary outcome measure is time to Target Lesion Primary Patency (TLPP). This will be measured in days post treatment fistuloplasty.

Secondary outcome measures
The secondary outcomes, as listed in 1.1.1, will be measured as follows:

1. Late lumen loss (mm); the difference between the diameter of the lesion at the completion fistulogram II (baseline) and at the protocol fistulogram (6 months)
2. Rate of binary angiographic re-stenosis (%); at the protocol fistulogram (6 months)
3. Time to loss of access circuit primary patency (days post treatment fistuloplasty)
4. Time to loss of access circuit cumulative patency (days post treatment fistuloplasty)
5. Procedural success (yes; no); stenosis ≤30% at completion fistulogram II (baseline)
6. Thrombosis events (number); recorded as fistula interventions throughout the trial
7. Fistula interventions (number); recorded throughout the trial
8. Adverse events (number); recorded throughout the trial
9. Patient quality of life; EQ-5D and POS-S Renal scores

Adverse events
The following adverse event measures will be collected at 6 and 12 months post randomisation, and at withdrawal, where applicable:

- Adverse Event (Oedema of hand or arm; Pseudoaneurysm; Haematoma; Distal Ischaemia; Neurological complications; Infection localised to fistula; Central venous catheter insertions; other)
- Duration of event (days)
- Intensity (mild; moderate; severe)
- Outcome (resolved; resolved with sequelae; ongoing; death; unknown)
- Related to study intervention (definite; probable; possible; remote; none)
- Serious Adverse Event (yes; no)
- Ongoing at end of study (yes; no)

Please refer to section 2 for the schedule of assessments and measures.

1.1.9 Sample size estimation (including clinical significance)

For the definition of the survival curve in the placebo balloon group, we assumed target lesion primary patency of 61%, 42%, and 35% at 6, 12 and 24 months respectively. This was consistent with published results {Bountouris:2014dy, Tessitore:2003ty} and with our own audit data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect

size {Katsanos:2012hd} found a HR of 0.3 for Target Lesion Primary Patency at 6 months; however, the confidence interval was broad and the effect size is expected to be closer to the null when AVGs are excluded. Based on these assumptions, it is expected that the paclitaxel coated balloon group will show 78%, 65%, and 59% survival of TLPP at 6, 12 and 24 months respectively. Recruiting 211 patients, with variable follow up, a minimum follow up of 1 year, and three interim analyses, will provide 94% power to detect a statistically significant difference between the two groups in TLPP survival with 2-sided 5% type I error rate. It is expected that 108 patients will experience fistula failure during the follow up period, 66 in the control arm, and 42 in the intervention arm.

The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, which would result in 6 patients in the treatment arm, and 3 in the control arm. We have planned for a recruitment rate of 2 patients per month (ppm) during the first three months, 8 ppm up to 7 months, and 12 ppm onwards. The expected accrual duration will be 22 months, and the maximum study duration (including follow-up) 34 months.

1.1.10 Brief description of proposed analyses

Analyses will be carried out by the trial statistician (ER) once the database has been locked. Data will be analysed with an intention-to-treat approach (i.e. analyse all those with data in groups as randomised irrespective of treatment received).

There will be descriptives statistics reported on the measures mentioned in 1.1.8, with an aim to comparing the treatment arms, and to review the patient demographics.

For the primary analysis, to test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival, Cox-Proportional Hazards regression will be used. This will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates; which are listed in detail in section 1.3.2.

Effects on secondary outcomes will be analysed using the same strategy for time-to-event variables, and generalized linear models for binary and continuous outcome measures, adjusting for the effects of relevant covariates when appropriate.

Interim analysis of the primary outcome will be performed three times throughout the study, based on the cumulative number of failures of the treatment area.

Further details of the analyses are given later on in this document.

Data summaries and analyses will be carried out in Stata 14.0.

1.2 Data analysis plan – Data description

1.2.1 Recruitment, eligibility and representativeness of patients

A CONSORT flow chart will be constructed – see Figure 1. The number of patients will be summarised using the following categories: total number of patients screened; eligible; consenting; and randomised.

Then by treatment arm: patients compliant and non-compliant with intervention; continuing through the trial; withdrawing; lost to follow-up; and excluded or analysed.

Compliance (adherence) is defined as receiving the following procedures: plain balloon fistuloplasty; completion fistulogram I; study treatment fistuloplasty; and completion fistulogram II.

A summary of the number of patients compliant with the study treatment will be provided and stratified by study centre.

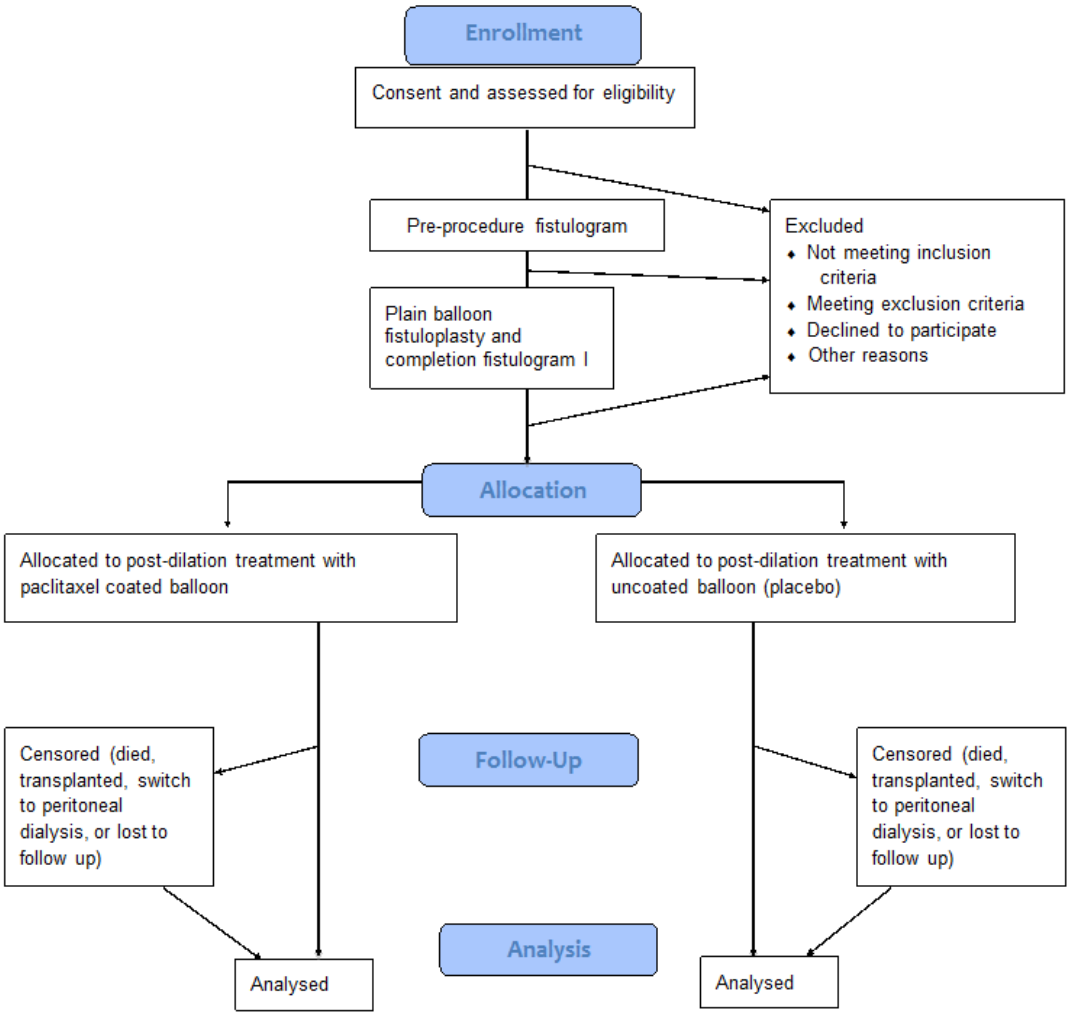

Figure 1. Template CONSORT diagram for PAVE trial

1.2.2 Baseline comparability of randomised groups

All baseline variables listed under measures in section 1.1.8 will be reported by trial arm and overall. They will be grouped into patient demographics and patient clinical information, and reported as: minimums and maximums, means and standard deviation, medians and quartiles for continuous variables as appropriate; and frequencies and proportions for categorical variables. No significance testing will be used to test baseline differences between the trial arms.

1.2.3 Adherence to allocated treatment and treatment fidelity

Adherence to allocated treatment (compliant versus non-compliant), as described in 1.2.1, and the reasons for not completing the treatment process will be summarised using the treatment fistuloplasty form. Adherence will be compared between trial arm using baseline variables; and the reasons for withdrawal from treatment will be summarised.

1.2.4 Loss to follow-up and other missing data

Withdrawal from trial follow-up (attrition rate) will be reported by intervention group, including reasons for withdrawal. The proportions of participants missing each variable will be summarised in each arm and at each study visit.

If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. Patients with TLPP at the end of follow up will be considered censored, as will those who receive a renal transplant, switch to peritoneal dialysis or are lost to follow up before the study end.

The baseline characteristics and adverse events of patients lost to follow up will be compared to those with complete follow up data. The relationship between these and missing data will be investigated graphically to see if baseline characteristics or adverse events predict missing, i.e. drop-outs are not random.

1.2.5 Adverse event reporting

Adverse events (AE), adverse reactions (AR), serious adverse events (SAE) and serious adverse reactions (SAR) will be summarised by trial arm and overall.

1.2.6 Assessment of outcome measures (unblinding)

Outcome assessors and the trial statistician are being kept blind to treatment allocation.

1.2.7 Descriptive statistics for outcome measures

The primary and secondary outcomes as listed in section 1.1.8 will be described by treatment group and time point. Means and standard deviations or medians and interquartile ranges will be used for continuous variables, where relevant; this will check whether continuous outcomes can be assumed normally distributed. Kaplan-Meier plots,

hazard-ratio and its confidence interval will be used to describe the time to event results. Frequencies and proportions will be used to describe binary variables.

1.3 Data analysis plan – Inferential analysis

1.3.1 Aims of formal inferences

The formal statistical analyses will estimate the differences in relevant variables (time to event, quality of life) between patients randomised to the paclitaxel-coated balloon angioplasty compared to high-pressure placebo balloon angioplasty, by intention to treat.

As mentioned in section 1.2.4, for the primary outcome and other time to event variables, patients lost to follow-up will be right censored; this means they are counted as not having experienced end of target lesion primary patency, or the relevant event, for the period of time we have data on them. If dropout is related to both outcome and treatment, then dropouts may bias the results.

Group difference estimates and associated 95% confidence intervals will be reported. The trial statistician will remain blind until the main analyses have been completed. The overall significance level will be 5% (two-sided) for the primary and secondary outcomes. Significance level of final analysis of primary outcome will be determined by the alpha spending function used to plan interim analyses.

Details on the methods for handling missing data are given in sections 1.3.8.

Sensitivity analyses will be used to assess the robustness of conclusions; please refer to section 1.4 for details of the planned sensitivity and subgroup analyses.

1.3.2 Analysis of the primary outcome

The analysis population will include all patients randomised with sufficient information to carry out the analysis, i.e. complete primary outcome data and minimisation factors. The primary outcome is time to end of target lesion primary patency (TLPP); measured as days post randomisation. For the purpose of the primary outcome analysis, this will be taken as recorded by the target lesion primary patency form.

Expected time to end of TLPP will be calculated using the hazard ratio estimated by the model explained below. Survival analysis methods will be used to compare the primary outcome for the two groups as this can factor in censoring and time.

Kaplan-Meier plots will be used to graphically illustrate and compare the observed probabilities of target lesion primary patency past certain times in the trial period, taking into account censoring, for the two trial arms. This is a non-parametric estimate of the survival function over the analysis time, and will also be used to check the Cox proportionality assumption – see section 1.3.10.

Cox-Proportional Hazards regression will be used to model the effect of predictors and covariates on the hazard rate and estimate the relative risk by trial arm. This will be compared to an initial estimate from the null model where the model will be fitted without any covariates. Model components included in the primary model will be a baseline hazard function that is unspecified but positive; previous radiological intervention in the access circuit; trial centre; trial arm; observed study time (length of time between patient entering and exiting study); and a trial arm*observed time interaction term. The interaction term allows for variable follow-up time effects.

A secondary adjusted analysis will be fit to evaluate the impact of baseline covariates on the size of the treatment effect. The covariates considered will be: baseline characteristics (ethnicity; age; diabetes diagnosis; and smoking history) and clinical variables at baseline (total time on haemodialysis; time since end stage kidney failure; type of native fistula; previous circuit intervention; and location of stenosis).

The relationship between baseline variables and missing outcome data will be assessed using logistic regression with an outcome variable that represents whether outcome data are present or missing. Should any baseline variables be predictive of missing then these will be included in the primary analysis Cox regression models as further covariates.

1.3.3 Interim analysis

Interim analysis of the primary outcome will be performed three times throughout the study, based on the cumulative number of failures in the primary outcome, i.e. after 27, 54 and 81 events, expected approximately at 9, 14 and 19 months of study under the null, and at months 11, 17, and 23 under the alternative hypothesis. Group sequential stopping boundaries have been calculated using a Lan-de-Mets spending function (with O'Brian-Fleming parameters), to allow early stopping for rejection of the null or the alternative hypotheses. Stopping in case of boundary crossing is non-binding and will be discussed with the DMEC members during a closed session that does not include any trial members who are blinded.

The Hazard Ratio used to evaluate the crossing of stopping boundaries will be calculated with a Cox-proportional hazards regression that includes centre, and presence or absence of previous interventions as covariates, as well as treatment group as independent variable of interest.

Stopping boundaries are displayed in the figure below:

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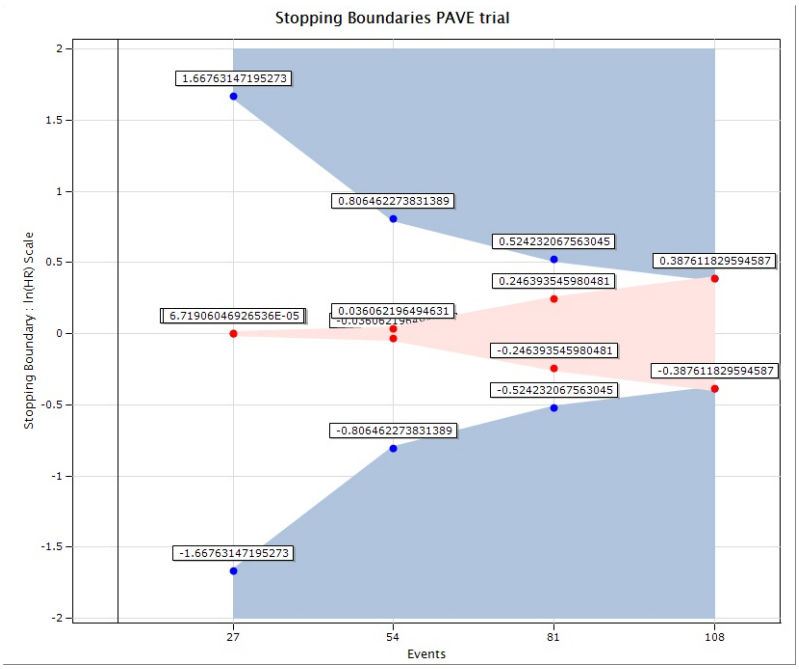

The table below shows further details of the stopping boundaries, including expected probability of crossing at each interim, and cumulative Alpha and Beta spent.

Look #	Info. Fraction	Events	Cum. α Spent	Cum. β Spent	Boundaries			
					Efficacy Boundary		Futility Boundary	
					Upper	Lower	Upper	Lower
1	0.25	27	0	0	5.3	0.189	1	1
2	0.5	54	0.003	0.004	2.24	0.446	1.037	0.965
3	0.75	81	0.019	0.024	1.689	0.592	1.279	0.782
4	1	108	0.05	0.059	1.473	0.679	1.473	0.679

Look #	Sample Size		Analysis Time		Incremental Boundary Crossing Probabilities					
					Under H0: ln(λ_t/λ_c) = 1			Under H1: ln(λ_t/λ_c) = 0.49...		
	Under H0	Under H1	Under H0	Under H1	Efficacy		Futility	Efficacy		Futility
					Upper	Lower		Upper	Lower	
1	91	106	9.483	10.968	0	0	0	0	0.006	0
2	140	163	14.522	16.985	0.002	0.002	0.105	0	0.333	0.004
3	185	211	19.213	22.651	0.008	0.008	0.633	0	0.44	0.02
4	211	211	23.95	33.792	0.014	0.014	0.214	0	0.162	0.035

Stopping boundaries in the table are expressed in the HR scale.
Test statistics for interim analysis will be calculated with standard statistics software packages (R or Stata), and entered into the interim monitoring tool of the East software in order to check crossing of boundaries, and calculate effect size and conditional power.

Interim analyses will be programmed by the trial statistician, but run and summarised by an independent statistician.

1.3.4 Analysis of secondary outcomes

Secondary patient outcomes relating to time-to-event variables, for example, time to end of access circuit primary patency, will be analysed using Cox regression models in a similar method to above.

Continuous variables such as POS-S Renal score for quality of life, will be checked for normality, transformed if necessary and analysed using linear regression models. Otherwise, they will be analysed using a Wilcoxon-signed-rank test for independent samples. Logistic regression models will be used for binary secondary outcomes, for example, procedural success (rate of binary angiographic re-stenosis ≥50%) at the six month protocol fistulogram.

Similarly to the primary outcome analysis, covariates considered in the models will include: baseline measure of outcome variable, where applicable; minimisation factors; trial arm; and time in study. An interaction term will also be included between observed study time and study treatment, as above.

1.3.5 Stratification and clustering

Randomisation is on the patient level, minimising on radiologist performing the study treatment and previous radiological intervention to treatment area or not; therefore these variables will be included as covariates in the modelling process, as mentioned in section 1.3.2. However, the data should not have a clustered structure so this does not need to be accounted for.

1.3.6 Missing items in scales and subscales

The number (%) with complete data will be reported. The ideal approach would be to use missing value guidance provided for scales.

1.3.7 Missing baseline data

We do not anticipate missing values in pre-randomisation variables. However, if we encounter missing baseline values then these can be singly imputed according to White and Thompson[3] without incurring bias of the treatment effect estimate.

1.3.8 Censoring and missing outcome data

For time to event outcomes, patient data is considered censored when the patient is withdrawn from follow-up, i.e. it is only known that the amount of time to event for that patient is greater than some value. Censoring will also happen at the end of the study, if the patient does not experience the primary endpoint before end of follow-up. In the analysis, the censored observations will be included in the number of patients at risk in respect to their observed study time (survival time).

For non-time to event outcomes, missing post-randomisation assessments will be dealt with by fitting generalised mixed models to all the available data using maximum likelihood methods. Such an approach provides valid inferences under the assumption that the missing data mechanism is ignorable (or MAR). This allows for missingness at later times to be predicted by outcome values at earlier times. If post treatment variables such as compliance with study procedures are found to be predictive of drop out, multiple imputation will be considered.

1.3.9 Method for handling multiple comparisons

Analysis of secondary outcomes is considered exploratory, and therefore there will be no correction for multiple testing. However, care should be given to the interpretation of inference for the numerous secondary outcomes and it may be necessary to assess the agreement between similar outcome measures. Cohen's Kappa statistic and/or Spearman's rank correlation coefficients may be used to test for inter-participant reliability and to measure the degree of linear association between two outcomes. For example, angiographically determined late lumen loss and the rate of binary angiographic re-stenosis would be expected to be highly predictive of one another.

1.3.10 Method for handling non-compliance

In addition to the primary intention-to-treat analysis the effect of actually receiving treatment as defined in the protocol will also be estimated.

There is not expected to be a problem with non-compliance due to the design of the trial.

1.3.11 Model assumption checks

In order to assess the adequacy of the Cox regression models for the primary outcome and time-to-event secondary outcomes, the main assumption to test for is proportionality; the Kaplan-Meier plots will be used to check if the curves for the two trial arms are the same shape, and if the separation of the curves remains proportionate throughout the analysis period.

In addition, time-dependent covariates will be generated by creating interactions of the predictors and function of survival time; if these are significant then the predictors are not proportional.

If the assumption for proportionality is violated then the consequence this has on the results can be checked. The Cox model can be stratified according to the variables with non-proportional hazards to see whether that changes the hazard ratios for the variables of interest; if it still does, then it may be necessary to use an alternative model. One parametric alternative is the Royston-Parmar model, which is more flexible and can fit a non-proportional hazards model.

For the other secondary outcomes regression residuals will be plotted to check for normality and outliers, where applicable.

1.4 Sensitivity analyses

1.4.1 Planned sensitivity analyses

A sensitivity analysis will be performed using adjudicated data from the core lab readings, in comparison to the primary analysis where the events reported in the trial will be used. This will assess the robustness of the trial findings by clarifying whether the primary analysis conclusions are impacted by any methodological issues, such as outcome definitions.

1.4.2 Planned subgroup analyses

Subgroup analyses will be carried out to assess whether the observed effect is consistent across patient categories; to do this, an interaction term will be included in the Cox proportional hazards model between the exposure (study treatment group) and the subgroup variable.

The planned subgroups will be: second minimisation factor (previous radiological intervention to the treatment area or not); smoking history (current smoker, former smoker, never smoked); baseline diabetes diagnosis (yes, no); current total time on haemodialysis (quartiles); total time since end stage kidney failure (quartiles); type of native fistula (Radio-cephalic, Brachio-cephalic, Basilic vein transposition, Ulnar-cephalic); and location of stenosis (juxta-anastomotic, venous segment, cephalic arch, between cephalic arch and thoracic inlet).

1.4.3 Competing risks analyses

To assess the influence of events that may prevent other events from being observed, competing risks analyses will be planned to adjust for these. Specifically, 'irrelevant' deaths and re-transplantations will be defined as competing risks rather than censored events. The cause of death will be checked from hospital notes and/or death certificates.

1.4.4 Exploratory analyses

This analysis plan does not cover secondary exploratory analysis. Exploratory mediator and moderator analyses may be performed after the primary trial data analysis.

1.5 Software

Data management: An online data collection system for clinical trials (MACRO; InferMed Ltd) will be used. This is hosted on a dedicated server at KCL and managed by the KCTU. The KCTU Data Manager will extract data periodically as needed and requests will usually be made by the trial statistician. There will be several database extracts throughout the trial for each DMEC Report, and a final extract after data lock. Data will be provided in comma separated (.csv) format.

Statistical analysis: Stata and or R will be used for data description and inferential analysis.

2 SCHEDULE OF ASSESSMENTS AND MEASURES

PAVE	Variable count	Enrolment	Treatment day (Day 0)	Day 1-3	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36	Ongoing
01. Registration form	5	X															
02. Eligibility form	14	X															
03. Medical History form	19	X															
04. Haematology and Biochemistry form	11	X		X	X	X											
05. Pre-procedure Fistulogram form	8		X														
06. Randomisation form	4		X														
07. Treatment Fistuloplasty form	46		X														
08. Fistula Intervention form (repeating)	32																X
09. Month 6 Fistula Function form	9					X											
10. Protocol Fistulogram form	11					X											
11. POS-S Renal questionnaire	25	X				X		X									
12. EQ-5D questionnaire	6	X				X		X									
13. Medications form	17	X			X	X	X	X	X	X	X	X	X	X	X	X	
14. Adverse Events form	9																X
15. Withdrawal form	5																X
16. Status form	5				X	X	X	X	X	X	X	X	X	X	X	X	
17. Loss of Patency form (repeating)	9																X

3 REFERENCE LIST

1. Bountouris:2014dy, Tessitore:2003ty 8
2. Katsanos:2012hd 8
3. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials 2005;24(7): 993–1007 15

PAVE Statistical Analysis Plan

Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access (PAVE)

A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel-assisted balloon angioplasty of venous stenosis in haemodialysis access

Statistical Analysis Plan

Version 2.0

Version 2.0 started: 26/09/2018

ISRCTN: 14284759

This SAP has been written based on Protocol V8.0

Trial Statistician: Emily Robinson

Signature Date 15/11/2018

Chief Investigator: Dr Michael Robson

Signature Date 14/05/2019

Trial Steering Committee Chair: Dr Richard Haynes

Signature Date 15/11/2018

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PAVE Statistical Analysis Plan

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PAVE Statistical Analysis Plan

1 QUANTITATIVE ANALYSIS PLAN

This document details the presentation and analysis strategy for the primary paper reporting results from the PAVE trial. Subsequent papers of a more exploratory nature will not be bound by this analysis plan but will be expected to follow the broad principles laid down for the principle paper(s). The principles are not intended to curtail exploratory analysis or to prohibit sensible statistical and reporting practices. Rather, they are intended to establish the primary scientific objective of the study, including the primary comparison and primary outcome and the strategy that will be followed as closely as possible, when analysing and reporting the trial.

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1.1 Description of the trial

This is a double-blind, multicentre RCT to assess the efficacy of additional paclitaxel-coated balloon angioplasty compared to high-pressure balloon angioplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

1.1.1 Principal research objectives to be addressed

The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.

Primary objective
To assess time to end of target lesion primary patency (TLPP) following study treatment angioplasty.

Secondary objectives
To assess the difference between the two groups in:

1. Angiographically determined late lumen loss
2. The rate of binary angiographic re-stenosis
3. Time to end of access circuit primary patency
4. Time to end of access circuit cumulative patency
5. Procedural success
6. Number of thrombosis events
7. Number of fistula interventions
8. Adverse events
9. Patient quality of life assessed by EQ-5D and POS-S Renal

A detailed description of trial objectives can be found in protocol section 2.1.

1.1.2 Trial design including blinding

The study is a double-blind multicentre randomised controlled trial, aiming to recruit 211 patients over a two-year period. Randomisation will be at the level of the individual participants, minimising on radiologist performing the study procedure; whether the patient has had a previous radiological intervention in the access circuit or not; and whether the patient is currently on haemodialysis. Follow up will be variable and for a minimum of one year; and all patients will continue in the study until the last patient has completed one year of follow up.

1.1.3 Method of allocation of groups

Recruitment and pre-screening procedures are described in the protocol sections 4.1-4.3. Once the patient has completed the pre-procedure fistulogram, high-pressure balloon fistuloplasty, and the completion fistulogram I, the radiologist will assess if the residual stenosis is ≤30%; if this is the case then the patient will proceed to randomisation.

Randomisation will take place via a web based randomisation service, hosted at the UKCRC registered clinical trials unit at KCL. Site staff will access the service via www.ctu.co.uk using a computer in the angiography room or an office nearby. It will be performed by the radiologist performing the study procedure, or their nominee, and each randomiser will have unique user access. Access will be provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed and relevant documentation regarding the individuals has been collected. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention.

As explained in 1.1.2, patients will be randomized using minimisation; this is performed with an 80% probability of allocating to the arm which reduces the imbalance. The allocation sequence will be generated dynamically so that the next allocation will only be generated and become known upon actioning a request from the study site staff. Once randomised, the system will automatically generate an email confirmation, which will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study: an unblind email is received by the trial manager and the radiologist who is performing the randomisation; and a blind email is received by the principal investigator and research nurses.

If it is not possible to use the randomisation system randomisation may occur using the toss of a coin in order to avoid losing the patient from the study. This should only be needed, if at all, in specific and rare situations such as the CTU server being inaccessible. This will be performed by two people with heads denoting drug-coated balloon, and tails denoting placebo. The CTU must be informed of the coin randomisation as soon as possible.

1.1.4 Duration of the treatment period

Study treatment is described in detail in the protocol section 4.5. This is a one-off treatment that is administered within one study visit. Any repeat intervention is considered an event and therefore the end of the follow up.

1.1.5 Frequency and duration of follow-up

Study assessments will take place every 3 months. Follow up will be variable but for a minimum of 1 year. These will involve a clinical assessment to take place either face-to-face or via a telephone conversation. Any face-to-face meetings will usually coincide with dialysis to avoid additional patient travel.

1.1.6 Visit windows

At the time of each 3-month study assessment, an allowance of one month will be given either side to measure follow-up. This one month visit window will be the same for recording data throughout the follow-up period.

1.1.7 Eligibility screening

Patients that may be eligible will be identified in a vascular access clinic and assessed by surgeons, specialist nurses and nephrologists. In order to confirm there is a significant stenosis prior to angiography, a duplex ultrasound is encouraged but is not mandatory. At least 24 hours after being given the patient information sheet and before entering the angiography room for the pre-procedure fistulogram, consent will be taken and eligibility criteria will be assessed.

Inclusion and exclusion criteria are described in sections 3.2 and 3.3 of the protocol.

The radiologist who will perform the pre-procedure fistulogram, high-pressure balloon fistuloplasty and completion fistulogram will be informed that the patient is potentially eligible for the study, and they will assess the remaining eligibility criteria.

1.1.8 Measures

Baseline
The following demographics will be measured at baseline:

- Age (years)
- Gender (male; female)
- Ethnicity (White; Black; Asian; Mixed; Other)

The following clinical details will be measured at medical history screening:

- Current diabetes diagnosis (yes; no)
- Patient smoking history (current smoker; former smoker; never smoked)
- Coronary artery disease (yes; no)
- Peripheral vascular disease (yes; no)
- Time since end-stage kidney failure (months)
- Previous renal transplant(s) (number)
- Total accumulated time with a functional renal transplant (months)
- Total accumulated time patient has spent on haemodialysisis (months)
- Total accumulated time patient has spent on peritoneal dialysis (months)
- Location of fistula (right arm; left arm)
- Type of native fistula (Radio-cephalic; Brachio-cephalic; Basilic vein transposition; Ulnar-cephalic)
- Time since fistula was formed (months)
- Time since fistula was first used (months)
- Current access circuit previously had a thrombosis (yes; no)
- Previous surgical interventions to the current access circuit (number)
- Previous fistuloplasties to the current access circuit (number)
- Primary indication for the index procedure (inadequate dialysis; poor fistula blood flow; prolonged bleeding; high venous pressures; low arterial pressure; difficulty needling; other evidence of fistula dysfunction)

The following clinical details will be measured at the pre-procedure fistulogram:

- Location of stenosis (juxta-anastamotic; venous segment; cephalic arch; after cephalic arch and not beyond the thoracic inlet; beyond the thoracic inlet)
- Degree of stenosis (5%)
- Length of stenosis (mm)
- Radiologist (initials)

The following clinical details will be measured at the treatment fistuloplasty:

- Index lesion vessel diameter (mm)
- Diameter of plain balloon used (mm)
- Length of plain balloon used (mm)
- Pressure to which used plain balloon was inflated (atm)
- Number of unsuccessful attempts at plain balloon fistuloplasty (0-2)
- Complications due to plain balloon fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Diameter of study treatment balloon used (mm)
- Length of study treatment balloon used (mm)
- Pressure to which study treatment balloon was inflated (atm)
- Complications of the study treatment fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Residual stenosis still 30% or less after study treatment (yes; no)

- Further fistuloplasty performed after study treatment (yes; no)
- Type of balloon from further fistuloplasty (Dorado; other)
- Diameter of balloon from further fistuloplasty (mm)
- Length of balloon from further fistuloplasty (mm)
- Residual stenosis 30% or less after further fistuloplasty (yes; no)
- Complications due to further fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Radiologist (initials)

Primary outcome measures
The primary outcome measure is time to Target Lesion Primary Patency (TLPP). This will be measured in days post treatment fistuloplasty.

Secondary outcome measures
The secondary outcomes, as listed in 1.1.1, will be measured as follows:

1. Late lumen loss (mm); the difference between the diameter of the lesion at the completion fistulogram II (baseline) and at the protocol fistulogram (6 months)
2. Rate of binary angiographic re-stenosis (%); at the protocol fistulogram (6 months)
3. Time to loss of access circuit primary patency (days post treatment fistuloplasty)
4. Time to loss of access circuit cumulative patency (days post treatment fistuloplasty)
5. Procedural success (yes; no); stenosis ≤30% at completion fistulogram II (baseline)
6. Thrombosis events (number); recorded as fistula interventions throughout the trial
7. Fistula interventions (number); recorded throughout the trial
8. Adverse events (number); recorded throughout the trial
9. Patient quality of life; EQ-5D and POS-S Renal scores

Adverse events
The following adverse event measures will be collected at 6 and 12 months post randomisation, and at withdrawal, where applicable:

- Adverse Event (Oedema of hand or arm; Pseudoaneurysm; Haematoma; Distal Ischaemia; Neurological complications; Infection localised to fistula; Central venous catheter insertions; other)
- Duration of event (days)
- Intensity (mild; moderate; severe)
- Outcome (resolved; resolved with sequelae; ongoing; death; unknown)
- Related to study intervention (definite; probable; possible; remote; none)
- Serious Adverse Event (yes; no)
- Ongoing at end of study (yes; no)

Please refer to section 2 for the schedule of assessments and measures.

1.1.9 Sample size estimation (including clinical significance)

For the definition of the survival curve in the placebo balloon group, we assumed target lesion primary patency of 61%, 42%, and 35% at 6, 12 and 24 months respectively. This was consistent with published results (Bountouris, 2014; Tessitore, 2003) and with our own audit

data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect size; (Katsanos, 2012) found a HR of 0.3 for Target Lesion Primary Patency at 6 months, however, the confidence interval was broad and the effect size is expected to be closer to the null when AVGs are excluded. Based on these assumptions, it is expected that the paclitaxel coated balloon group will show 78%, 65%, and 59% survival of TLPP at 6, 12 and 24 months respectively. Recruiting 211 patients, with variable follow up, a minimum follow up of 1 year, and three interim analyses, will provide 94% power to detect a statistically significant difference between the two groups in TLPP survival with 2-sided 5% type I error rate. It is expected that 108 patients will experience fistula failure during the follow up period, 66 in the control arm, and 42 in the intervention arm.

The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, which would result in 6 patients in the treatment arm, and 3 in the control arm. We have planned for a recruitment rate of 2 patients per month (ppm) during the first three months, 8 ppm up to 7 months, and 12 ppm onwards. The expected accrual duration will be 22 months, and the maximum study duration (including follow-up) 34 months.

1.1.10 Brief description of proposed analyses

Analyses will be carried out by the trial statistician (ER) once the database has been locked. Data will be analysed with an intention-to-treat approach (i.e. analyse all those with data in groups as randomised irrespective of treatment received).

There will be descriptives statistics reported on the measures mentioned in 1.1.8, with an aim to comparing the treatment arms, and to review the patient demographics.

For the primary analysis, to test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival, Cox-Proportional Hazards regression will be used. This will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates; which are listed in detail in section 1.3.2.

Effects on secondary outcomes will be analysed using the same strategy for time-to-event variables, and generalized linear models for binary and continuous outcome measures, adjusting for the effects of relevant covariates when appropriate.

Interim analysis of the primary outcome will be performed up to three times throughout the study, based on the cumulative number of failures of the treatment area.

Further details of the analyses are given later on in this document.

Data summaries and analyses will be carried out in Stata 14.0.

1.2 Data analysis plan – Data description

1.2.1 Recruitment, eligibility and representativeness of patients

A CONSORT flow chart will be constructed – see Figure 1. The number of patients will be summarised using the following categories: total number of patients screened; eligible; consenting; and randomised.

Then by treatment arm: patients compliant and non-compliant with intervention; continuing through the trial; withdrawing; lost to follow-up; and excluded or analysed.

Compliance (adherence) is defined as receiving the following procedures: plain balloon fistuloplasty; completion fistulogram I; study treatment fistuloplasty; and completion fistulogram II.

A summary of the number of patients compliant with the study treatment will be provided and stratified by radiologist.

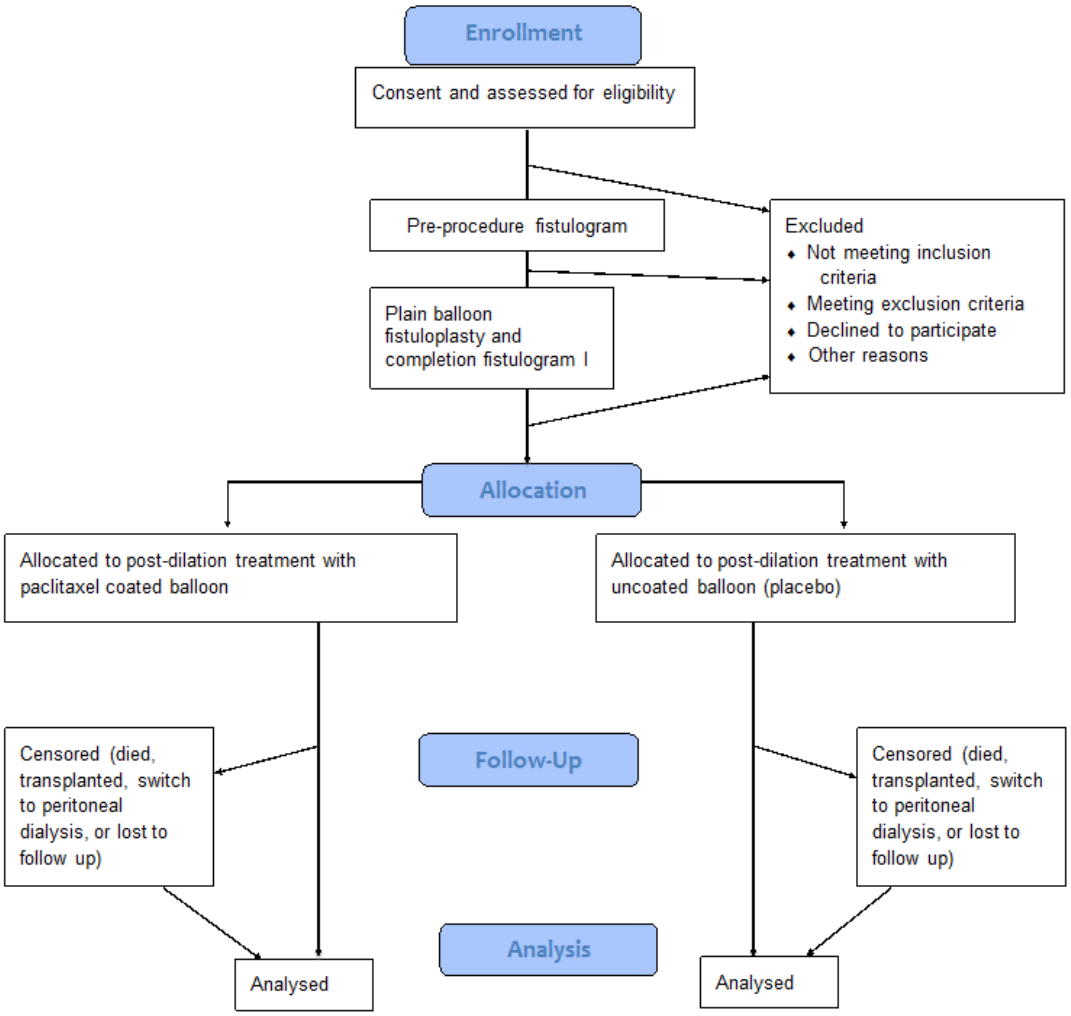


Figure 1. Template CONSORT diagram for PAVE trial

1.2.2 Baseline comparability of randomised groups

All baseline variables listed under measures in section 1.1.8 will be reported by trial arm and overall. They will be grouped into patient demographics and patient clinical information, and reported as: minimums and maximums, means and standard deviation, medians and quartiles for continuous variables as appropriate; and frequencies and proportions for categorical variables. No significance testing will be used to test baseline differences between the trial arms.

1.2.3 Adherence to allocated treatment and treatment fidelity

Adherence to allocated treatment (compliant versus non-compliant), as described in 1.2.1, and the reasons for not completing the treatment process will be summarised using the treatment fistuloplasty form. Adherence will be compared between trial arm using baseline variables; and the reasons for withdrawal from treatment will be summarised.

1.2.4 Loss to follow-up and other missing data

Withdrawal from trial follow-up (attrition rate) will be reported by intervention group, including reasons for withdrawal. The proportions of participants missing each variable will be summarised in each arm and at each study visit.

If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. Patients with TLPP at the end of follow up will be considered censored, as will those who receive a renal transplant, switch to peritoneal dialysis or are lost to follow up before the study end.

The baseline characteristics and adverse events of patients lost to follow up will be compared to those with complete follow up data. The relationship between these and missing data will be investigated graphically to see if baseline characteristics or adverse events predict missing, i.e. drop-outs are not random.

1.2.5 Adverse event reporting

Adverse events (AE), adverse reactions (AR), serious adverse events (SAE) and serious adverse reactions (SAR) will be summarised by trial arm and overall.

1.2.6 Assessment of outcome measures (unblinding)

Outcome assessors and the trial statistician are being kept blind to treatment allocation.

1.2.7 Descriptive statistics for outcome measures

The primary and secondary outcomes as listed in section 1.1.8 will be described by treatment group and time point. Means and standard deviations or medians and interquartile ranges will be used for continuous variables, where relevant; this will check whether continuous outcomes can be assumed normally distributed. Kaplan-Meier plots,

hazard-ratio and its confidence interval will be used to describe the time to event results. Frequencies and proportions will be used to describe binary variables.

1.3 Data analysis plan – Inferential analysis

1.3.1 Aims of formal inferences

The formal statistical analyses will estimate the differences in relevant variables (time to event, quality of life) between patients randomised to the paclitaxel-coated balloon angioplasty compared to high-pressure placebo balloon angioplasty, by intention to treat.

As mentioned in section 1.2.4, for the primary outcome and other time to event variables, patients lost to follow-up will be right censored; this means they are counted as not having experienced end of target lesion primary patency, or the relevant event, for the period of time we have data on them. If dropout is related to both outcome and treatment, then dropouts may bias the results.

Group difference estimates and associated 95% confidence intervals will be reported. The trial statistician will remain blind until the main analyses have been completed. The overall significance level will be 5% (two-sided) for the primary and secondary outcomes. Significance level of final analysis of primary outcome will be determined by the alpha spending function used to plan interim analyses.

Details on the methods for handling missing data are given in sections 1.3.8.

Sensitivity analyses will be used to assess the robustness of conclusions; please refer to section 1.4 for details of the planned sensitivity and subgroup analyses.

1.3.2 Analysis of the primary outcome

The analysis population will include all patients randomised with sufficient information to carry out the analysis, i.e. complete primary outcome data and minimisation factors. The primary outcome is time to end of target lesion primary patency (TLPP); measured as days post randomisation. For the purpose of the primary outcome analysis, this will be taken as recorded by the target lesion primary patency form.

Expected time to end of TLPP will be calculated using the hazard ratio estimated by the model explained below. Survival analysis methods will be used to compare the primary outcome for the two groups as this can factor in censoring and time.

Kaplan-Meier plots will be used to graphically illustrate and compare the observed probabilities of target lesion primary patency past certain times in the trial period, taking into account censoring, for the two trial arms. This is a non-parametric estimate of the survival function over the analysis time, and will also be used to check the Cox proportionality assumption – see section 1.3.10.

Cox-Proportional Hazards regression will be used to model the effect of predictors and covariates on the hazard rate and estimate the relative risk by trial arm. This will be compared to an initial estimate from the null model where the model will be fitted without any covariates. Model components included in the primary model will be a baseline hazard function that is unspecified but positive; previous radiological intervention in the access circuit; on haemodialysis at randomisation; trial arm; observed study time (length of time between patient entering and exiting study); and a trial arm*observed time interaction term. The interaction term allows for variable follow-up time effects.

A secondary adjusted analysis will be fit to evaluate the impact of baseline covariates on the size of the treatment effect. The covariates considered will be: baseline characteristics (ethnicity; age; diabetes diagnosis; and smoking history) and clinical variables at baseline (total time on haemodialysis; time since end stage kidney failure; type of native fistula; previous circuit intervention; and location of stenosis).

The relationship between baseline variables and missing outcome data will be assessed using logistic regression with an outcome variable that represents whether outcome data are present or missing. Should any baseline variables be predictive of missing then these will be included in the primary analysis Cox regression models as further covariates.

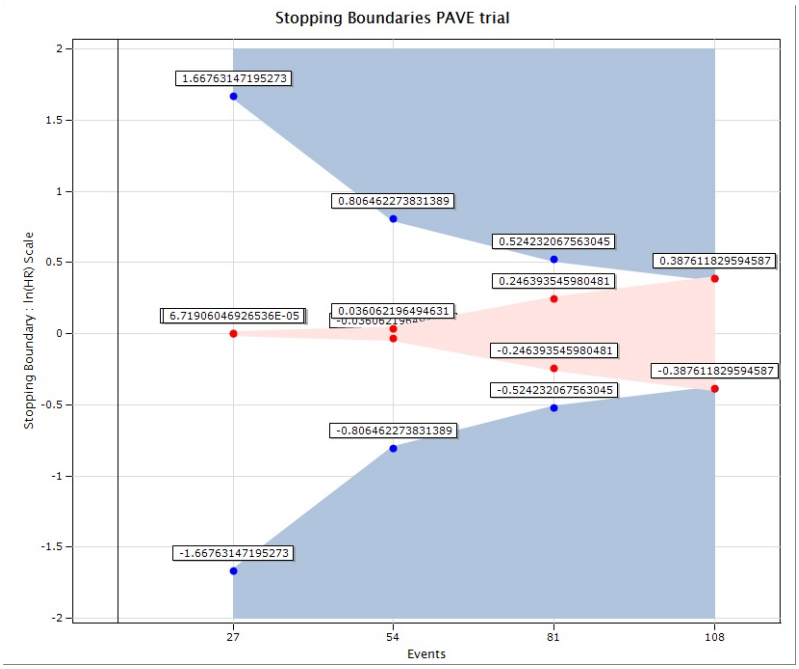
1.3.3 Interim analysis

Interim analysis of the primary outcome will be performed up to three times throughout the study, based on the cumulative number of failures in the primary outcome, i.e. after 27, 54 and 81 events, expected approximately at 9, 14 and 19 months of study under the null, and at months 11, 17, and 23 under the alternative hypothesis. Group sequential stopping boundaries have been calculated using a Lan-de-Mets spending function (with O'Brian-Fleming parameters), to allow early stopping for rejection of the null or the alternative hypotheses. Stopping in case of boundary crossing is non-binding and will be discussed with the DMEC members during a closed session that does not include any trial members who are blinded.

The Hazard Ratio used to evaluate the crossing of stopping boundaries will be calculated with a Cox-proportional hazards regression that includes presence or absence of previous interventions and currently on haemodialysis or not as covariates, as well as treatment group as independent variable of interest.

Stopping boundaries are displayed in the figure below:

PAVE Statistical Analysis Plan



The table below shows further details of the stopping boundaries, including expected probability of crossing at each interim, and cumulative Alpha and Beta spent. Stopping boundaries in the table are expressed in the HR scale.

Look #	Info. Fraction	Events	Cum. α Spent	Cum. β Spent	Boundaries			
					Efficacy Boundary		Futility Boundary	
					Upper	Lower	Upper	Lower
1	0.25	27	0	0	5.3	0.189	1	1
2	0.5	54	0.003	0.004	2.24	0.446	1.037	0.965
3	0.75	81	0.019	0.024	1.689	0.592	1.279	0.782
4	1	108	0.05	0.059	1.473	0.679	1.473	0.679

Look #	Sample Size		Analysis Time		Incremental Boundary Crossing Probabilities					
					Under H0: ln(λ_t/λ_c) = 1			Under H1: ln(λ_t/λ_c) = 0.49...		
	Under H0	Under H1	Under H0	Under H1	Efficacy		Futility	Efficacy		Futility
					Upper	Lower		Upper	Lower	
1	91	106	9.483	10.968	0	0	0	0	0.006	0
2	140	163	14.522	16.985	0.002	0.002	0.105	0	0.333	0.004
3	185	211	19.213	22.651	0.008	0.008	0.633	0	0.44	0.02
4	211	211	23.95	33.792	0.014	0.014	0.214	0	0.162	0.035

Test statistics for interim analysis will be calculated with standard statistics software packages (R or Stata).

Interim analyses will be programmed by the trial statistician, and run and using the partially blinded randomisation sequence (trial arm numbers 1 or 2). The results will be presented to the DMEC in a partially blind report, and full unblinding of the code will only be provided to the members if they request it.

1.3.4 Analysis of secondary outcomes

Secondary patient outcomes relating to time-to-event variables, for example, time to end of access circuit primary patency, will be analysed using Cox regression models in a similar method to above.

Continuous variables such as POS-S Renal score for quality of life, will be checked for normality, transformed if necessary and analysed using linear regression models. Otherwise, they will be analysed using a Wilcoxon-signed-rank test for independent samples. Logistic regression models will be used for binary secondary outcomes, for example, procedural success (rate of binary angiographic re-stenosis ≥50%) at the six month protocol fistulogram.

Similarly to the primary outcome analysis, covariates considered in the models will include: baseline measure of outcome variable, where applicable; minimisation factors; trial arm; and time in study. An interaction term will also be included between observed study time and study treatment, as above.

1.3.5 Stratification and clustering

Randomisation is on the patient level, minimising on radiologist performing the study treatment and previous radiological intervention to treatment area or not; therefore these variables will be included as covariates in the modelling process, as mentioned in section 1.3.2. However, the data should not have a clustered structure so this does not need to be accounted for.

1.3.6 Missing items in scales and subscales

The number (%) with complete data will be reported. The ideal approach would be to use missing value guidance provided for scales.

1.3.7 Missing baseline data

We do not anticipate missing values in pre-randomisation variables. However, if we encounter missing baseline values then these can be singly imputed without incurring bias of the treatment effect estimate (White & Thompson, 2005).

1.3.8 Censoring and missing outcome data

For time to event outcomes, patient data is considered censored when the patient is withdrawn from follow-up, i.e. it is only known that the amount of time to event for that patient is greater than some value. Censoring will also happen at the end of the study, if the patient does not experience the primary endpoint before end of follow-up. In the analysis,

the censored observations will be included in the number of patients at risk in respect to their observed study time (survival time).

For non-time to event outcomes, missing post-randomisation assessments will be dealt with by fitting generalised linear models to all the available data using maximum likelihood methods. Such an approach provides valid inferences under the assumption that the missing data mechanism is ignorable (or MAR). This allows for missingness at later times to be predicted by outcome values at earlier times. However, if post treatment variables such as compliance with study procedures are found to be predictive of drop out, multiple imputation will be considered.

1.3.9 Method for handling multiple comparisons

Analysis of secondary outcomes is considered exploratory, and therefore there will be no correction for multiple testing. However, care should be given to the interpretation of inference for the numerous secondary outcomes and it may be necessary to assess the agreement between similar outcome measures. Cohen's Kappa statistic and/or Spearman's rank correlation coefficients may be used to test for inter-participant reliability and to measure the degree of linear association between two outcomes. For example, angiographically determined late lumen loss and the rate of binary angiographic re-stenosis would be expected to be highly predictive of one another.

1.3.10 Method for handling non-compliance

In addition to the primary intention-to-treat analysis the effect of actually receiving treatment as defined in the protocol will also be estimated.

There is not expected to be a problem with non-compliance due to the design of the trial.

1.3.11 Model assumption checks

In order to assess the adequacy of the Cox regression models for the primary outcome and time-to-event secondary outcomes, the main assumption to test for is proportionality; the Kaplan-Meier plots will be used to check if the curves for the two trial arms are the same shape, and if the separation of the curves remains proportionate throughout the analysis period.

In addition, time-dependent covariates will be generated by creating interactions of the predictors and function of survival time; if these are significant then the predictors are not proportional.

If the assumption for proportionality is violated then the consequence this has on the results can be checked. The Cox model can be stratified according to the variables with non-proportional hazards to see whether that changes the hazard ratios for the variables of interest; if it still does, then it may be necessary to use an alternative model. One parametric alternative is the Royston-Parmar model, which is more flexible and can fit a non-proportional hazards model.

For the other secondary outcomes regression residuals will be plotted to check for normality and outliers, where applicable.

1.4 Sensitivity analyses

1.4.1 Planned sensitivity analyses

A sensitivity analysis will be performed using adjudicated data from the core lab readings, in comparison to the primary analysis where the events reported in the trial will be used. This will assess the robustness of the trial findings by clarifying whether the primary analysis conclusions are impacted by any methodological issues, such as outcome definitions.

1.4.2 Planned subgroup analyses

Subgroup analyses will be carried out to assess whether the observed effect is consistent across patient categories; to do this, an interaction term will be included in the Cox proportional hazards model between the exposure (study treatment group) and the subgroup variable.

The planned subgroups will be: second minimisation factor (previous radiological intervention to the treatment area or not); smoking history (current smoker, former smoker, never smoked); baseline diabetes diagnosis (yes, no); current total time on haemodialysis (quartiles); total time since end stage kidney failure (quartiles); type of native fistula (Radio-cephalic, Brachio-cephalic, Basilic vein transposition, Ulnar-cephalic); and location of stenosis (juxta-anastomotic, venous segment, cephalic arch, between cephalic arch and thoracic inlet).

1.4.3 Competing risks analyses

To assess the influence of events that may prevent other events from being observed, competing risks analyses will be planned to adjust for these. Specifically, 'irrelevant' deaths and re-transplantations will be defined as competing risks rather than censored events. The cause of death will be checked from hospital notes and/or death certificates.

1.4.4 Exploratory analyses

This analysis plan does not cover secondary exploratory analysis. Exploratory mediator and moderator analyses may be performed after the primary trial data analysis.

1.5 Software

Data management: An online data collection system for clinical trials (MACRO; InferMed Ltd) will be used. This is hosted on a dedicated server at KCL and managed by the KCTU. The KCTU Data Manager will extract data periodically as needed and requests will usually be made by the trial statistician. There will be several database extracts throughout the trial for each DMEC Report, and a final extract after data lock. Data will be provided in comma separated (.csv) format.

Statistical analysis: Stata and or R will be used for data description and inferential analysis.

1.6 Changes to version

1 Since Version 1.0 the Trial Manager(s) have changed, and this has been updated
2 Due to the recruitment period taking longer than planned, and including more hospital sites than originally expected, clarification has been made to the following sections in relation to minimisation factors, duration of trial follow-up, and frequency of interim analysis:
    - 1.1.2
    - 1.1.5
    - 1.1.6
    - 1.1.10
    - 1.2.1
    - 1.3.2
    - 1.3.3
    - 1.3.8

2 SCHEDULE OF ASSESSMENTS AND MEASURES

PAVE	Variable count	Enrolment	Treatment day (Day 0)	Day 1-3	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36	Ongoing
01. Registration form	5	X															
02. Eligibility form	14	X															
03. Medical History form	19	X															
04. Haematology and Biochemistry form	11	X		X	X	X											
05. Pre-procedure Fistulogram form	8		X														
06. Randomisation form	4		X														
07. Treatment Fistuloplasty form	46		X														
08. Fistula Intervention form (repeating)	32																X
09. Month 6 Fistula Function form	9					X											
10. Protocol Fistulogram form	11					X											
11. POS-S Renal questionnaire	25	X				X		X									
12. EQ-5D questionnaire	6	X				X		X									
13. Medications form	17	X			X	X	X	X	X	X	X	X	X	X	X	X	
14. Adverse Events form	9																X
15. Withdrawal form	5																X
16. Status form	5				X	X	X	X	X	X	X	X	X	X	X	X	
17. Loss of Patency form (repeating)	9																X

3 References

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